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HEPATOLENTICULAR DEGENERATION

Analysis of Dyskinetic Phenomena; Relation of Degree of Hepatic Damage to Course of the Disease; Nervous Disorders in Ordinary Disease of the Liver

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THE CLINICAL diagnosis of hepatolenticular degeneration is made on the basis of the evaluation of the motor phenomena, the evidence of hepatic dysfunction and the presence of the ring of a pigment at the margin of the cornea. The classic descriptions of Wilson,[1] Westphal[2] and Strümpell[3] and the numerous subsequent reports make it possible to delimit this disease from other pathologic entities in the majority of cases. However, a detailed analysis of the dyskinetic symptoms is still wanting and the importance of liver function tests for diagnostic consideration is still under discussion.

The specificity of the clinical picture, as well as that of the pathologic changes in the brain stem, needs to be stressed again in the light of recent observations on nervous disorders associated with various hepatic diseases in man and in animals. A comparison of these conditions with hepatolenticular degeneration can be established only after careful analysis of the characteristic symptoms and elaboration of the important clinical and pathologic features.

PRESENT INVESTIGATION

Seven cases of hepatolenticular degeneration were studied at the Neurological Institute of New York in 1946 and 1947. The data are presented in an attempt to show the diversity of the clinical symptoms.

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1. Wilson, S. A. K.: Progressive Lenticular Degeneration: A Familial Nervous Disease Associated with Cirrhosis of the Liver, Brain **34**:295, 1912.

2. Westphal, C.: Ueber eine dem Bilde der cerebrospinalen Degeneration ähnliche Erkrankung des centralen Nervensystems ohne anatomischen Befund, Arch. f. Psychiat. **14**:87, 1883.

3. Strümpell, A.: (*a*) Ueber die Westphalsche Pseudosclerose und über diffuse Hirnsclerose, insbes. bei Kindern, Deutsche Ztschr. f. Nervenh. **12**:115, 1898; (*b*) Ein weiterer Beitrag zur Kenntnis der sogen. Pseudosclerose, ibid. **14**:348, 1899.

Varieties of motor phenomena were studied with the help of motion picture analysis. Slow motion pictures were used to define the course and pattern of the dyskinetic phenomena, as described elsewhere.[4] The extent of hepatic disturbance was evaluated from the results of liver function tests, and the course of the nervous disease was correlated with the severity of damage to the liver. Biopsy and necropsy material from the liver were used in some cases to determine the nature of the pathologic process in the liver. Clinical phenomena and pathologic changes associated with acquired disease of the liver were compared with those in hepatolenticular degeneration.

Case 1.—S. K., a man aged 34, entered the Neurological Institute in 1946. His birth and early development had been normal. He was the father of two apparently healthy children, aged 5 and 2 years. No history of familial disease was obtained.

Questioning failed to reveal any evidence of previous hepatic disease. At the age of 24 he had had a brief episode of violent trembling of both upper extremities. This lasted about a half-hour and was apparently precipitated by an emotional crisis. Otherwise he had been well until the age of 29, five years prior to his admission. At that time he first noted the insidious onset of a "tremor" of the right hand. The movements were described as "wild and swinging" and as appearing with effort. They disappeared entirely at rest and during sleep. Over a period of months, the involuntary movements gradually progressed to involve the entire right upper extremity. Within a year the left upper extremity was similarly involved, and shortly thereafter his speech became "quavering and interrupted." Gradually the head and neck showed abnormal motor activity, and nine months before his admission, four years after the onset, similar activity was noted in the right and then in the left lower extremity.

Physical Examination.—The general physical condition was normal. The liver and spleen were not palpable, and there was no evidence of obstruction of the portal venous system. Examination of the cornea revealed a greenish yellow ring, 2 mm. in diameter, at the limbus. Examination with the slit lamp confirmed the clinical impression of a Kayser-Fleischer ring.

Neurologic Examination.—There were no abnormalities except in the sphere of motor activity, as described in the motion picture analysis.

Laboratory Data.—The results of tests done on his admission (June 12) and repeated three months later (September 17) are shown in table 1. Roentgenograms of the skull and chest, as well as a barium sulfate study for esophageal varices, were reported as revealing no abnormality. The electroencephalogram was normal.

Motion Picture Analysis of the Dyskinetic Phenomena.—No spontaneous involuntary activity was present while the patient was standing, sitting or lying down. He seemed to be completely relaxed and showed no postural changes. Insecurity or disturbance of balance in walking or during the Romberg test was not apparent.

When the patient raised his arms from a position at rest on his knees to the horizontal position, the fast upward motion was secure. As soon as the horizontal position was reached, gross swaying of the arms, the forearms, the

4. Herz, E.: Die amyostatischen Unruheerscheinungen: Klinisch-kinematographische Analyse ihrer Kennzeichen und Begleiterscheinungen, Leipzig, Johannes Ambrosius Barth, 1931.

hands and the wrists appeared and became severer the longer the position was maintained. The movements occurred in all planes of space, and the pattern changed constantly. Repetition of similar patterns in the form of alternating motions was seen only occasionally. During the finger to nose test, the fast upward movement deviated only slightly from the straight line. As soon as the finger reached the nose, all parts of the upper extremity went into severe shaking. Slow motion pictures showed this activity to consist in completely irregular, swaying movements of the various joints in various directions. The direction of movements of the arm, forearm and hand changed constantly. Rolling movements of the arm and pronation and supination and flexion and extension of the forearm succeeded one another without any semblance of pattern.

TABLE 1.—*Laboratory Data in Case 1*

	June 12, 1946	Sept. 17, 1946
Complete blood count	Normal	Normal
Urine	Normal	Normal
Erythrocyte sedimentation rate	1 mm./hr.	.....
Phenolsulfonphthalein clearance test	15% 1 hr. 15% 2 hr.	.....
Dextrose tolerance test (oral), mg./100 cc.		
Fasting	97	.....
½ hr.	153 (2% in urine)	.....
1 hr.	118	.....
2 hr.	103	.....
2½ hr.	64	.....
Phosphorus inorganic, mg./100 cc.	2.3	2.8
Alkaline phosphatase, Bodansky units	2.9	3.3
Serum cholesterol, mg./100 cc.	143	.....
Combined	97.9	.....
Free	45.1	.....
Serum protein, Gm./100 cc.	6.9	7.6
Albumin, Gm./100 cc.	4.6	4.4
Globulin, Gm./100 cc.	2.3	3.2
Nonprotein nitrogen, mg./100 cc.	28	43
Serum bilirubin, mg./100 cc.	0.2	0.2
Cephalin flocculation test	Negative	.....
Prothrombin time	17.2 sec.	.....
Basal metabolic rate	—11%	.....
Bromsulphalein	Less than 5% retention of dye after 30 min.	Less than 5% retention of dye after 30 min.
Kline reaction	Negative	.....
Cerebrospinal fluid protein, mg./100 cc.	90	.....
Cells/cu. mm.	4	.....
Colloidal gold curve	Normal	.....
Wassermann reaction	Negative	.....

When the patient attempted to bring a glass filled with water to his mouth, this disturbance was greatly accentuated. During the upward motion, particularly when the patient tried to stabilize the position of the hand, the glass was turned in all directions of space.

Summary.—At the age of 29, impairment of motor activity of the left upper extremity developed gradually and progressed to involve the right lower extremity and both left extremities over a period of one year. Examination revealed no spontaneous involuntary activity, but there was severe discoordination, more pronounced during the maintenance of position than during the performance of active movements. Neither a history nor laboratory evidence of hepatic disease was found. A Kayser-Fleischer corneal ring was present. No family history of a

nervous disturbance was obtained. The course of the disease has been fairly static during the four years since the full development of the present symptoms.

CASE 2.—H. S., a man aged 31, was first seen in the winter of 1943. There was no evidence of any abnormality at birth or in the early development. No family history of nervous disease could be obtained. Investigation of the patient's medical history revealed an attack of "influenza" in 1919, without any symptoms of involvement of the central nervous system, and three or four infections of the upper respiratory tract each year. Symptoms indicative of hepatic disease had never been present.

In the spring of 1941, about eighteen months before his first admission, the patient, then 29, began to note difficulty in writing. This he described as due to "lack of control of the muscles." In about six months, he was unable to write with the right hand, and on his attempting to use the left hand the same lack of control became apparent. There was no muscular weakness or sensory disturbance. On his attempting to carry objects in the palm of the hand, the upper extremity would go into involuntary rhythmic flexion and extension at the elbow. During the spring of 1942 a disturbance in gait was noted. This consisted in the "toes digging into the ground." The only general systemic disorder was a vague malaise, lasting two or three days at a time and occurring at irregular intervals for the six to eight months prior to his admission.

Physical Examination.—The general physical condition was normal. Neither the liver nor the spleen was palpable. The neurologic abnormalities were limited to those which developed when the patient made attempts to perform motor activity. In walking, the patient tended to veer irregularly to the right or to the left. There was slight swaying in the Romberg test. A coarse tremor of the outstretched hands was noted. In attempting to write, he produced "large sweeps and curves," which rendered writing impossible.

Laboratory Investigation.—The laboratory findings at the time of his first admission (January 3) and on his second admission (Oct. 9, 1946) are shown in table 2. Roentgenograms of the chest and of the skull revealed nothing abnormal. The electroencephalogram was normal.

Course.—In the interval of thirty-four months before the patient's readmission, in October 1946, there had been an irregular progression of symptoms with some remissions. During the summer of 1945 the symptoms cleared greatly, and the patient gained weight. However, by the fall of 1945 the tremor had become more pronounced than ever and his speech was slower. In June 1946 he noted a tremor of his head, which became worse, and he lost 30 pounds (13.6 Kg.) in weight. On admission he also complained of excessive perspiration. A recheck of the history of hepatic symptoms revealed nothing of significance. The general physical, as well as the neurologic, examination showed nothing remarkable except for the dyskinetic phenomena.

Motion Picture Analysis of the Dyskinetic Phenomena.—Bilateral spontaneous involuntary activity was present in the upper and lower extremities and the face, neck and trunk. The distal parts of the extremities were most involved. Relatively fast irregular movements of choreatic character appeared in the hands and fingers and in the feet and toes. The pattern of the simple movements changed constantly. The irregular activity of the muscles of the neck and of the trunk was slightly more sustained, as in athetotic and dystonic movements. When the outstretched arms were held in the horizontal position, the same irregular activity was observed

in the hands and fingers, and to a lesser degree in the entire arm. When this position of the arm was maintained for some time, the choreatic finger movements increased in intensity. In addition, the whole outstretched arm, held stiff at the elbow, swayed in space and changed its position in various directions.

During the performance of the finger to nose test, the hyperkinesia became so severe that the patient, afraid of hurting himself, pressed his elbow against the chest or held onto his chin with his thumb. As soon as the elbow was bent, especially when the hand was held at the nose for some time, wild beating of the forearm began, the forearm being thrown in constantly changing directions. Varying movements of the arm at the shoulder and hand and finger movements complicated the pattern. Slow motion pictures revealed that the dyskinesia consisted of choreatic movements, in addition to irregular ataxic swaying of the various parts of the upper limb. During walking a slight increase in the spontaneous involuntary activity of the upper extremities was present. There was no insecurity in the Romberg position.

TABLE 2.—*Laboratory Findings in Case 2*

	Jan. 8, 1943	Oct. 9, 1946
Complete blood count	Normal	Normal
Urine	Normal	Normal
Blood sugar, mg./100 cc.	95	93
Kline reaction	Negative	Negative
Cerebrospinal fluid		
Protein, mg./100 cc.	41	42
Cells/cu. mm.	3	1
Colloidal gold curve	Normal	Normal
Wassermann reaction	Negative	Negative
Nonprotein nitrogen, mg./100 cc.	.....	38
Cephalin flocculation test	.....	+++
Bromsulphalein test	.....	Less than 5% retention of dye after 30 min.
Serum bilirubin, mg./100 cc.	.....	0.2
Serum phosphatase, Bodansky units	.....	2.9
Serum protein, Gm./100 cc.	.....	6.6
Albumin, Gm./100 cc.	.....	4.1
Globulin, Gm./100 cc.	.....	2.5
Inorganic phosphorus, mg./100 cc.	.....	2.8
Serum cholesterol, mg./100 cc.	.....	186
Combined	.....	130
Free	.....	56
Prothrombin time	.....	20.1 sec.
Bleeding time	.....	2 min. 15 sec.
Clotting time	.....	3 min.
Dextrose tolerance test, mg./100 cc.		
Fasting	87	86
½ hr.	106	152
1 hr.	92	320 (urine +++)
1½ hr.	87	71
2 hr.	62	82
2½ hr.	73	79

Biopsy of the Liver.—A specimen for biopsy was obtained during the patient's stay in the hospital. On laparotomy, the liver was observed to be somewhat smaller than normal, rather nodular and of a hobnail appearance. Microscopic study of the biopsy material showed infrequent glycogen nuclei in the hepatic cells, with coarse bands of connective tissue in the portal areas surrounding irregular groups of hepatic cells. The diagnosis was cirrhosis of the liver.

Immediately after the removal of the biopsy specimen, the respiration became greatly depressed, and the patient had to be given an oxygen-carbon dioxide mixture for twenty minutes. He recovered rapidly, and no further difficulty was encountered.

Summary.—The first symptoms of motor difficulty appeared at the age of 29. They interfered with the abilities to walk and write. At the time of the patient's first admission, eighteen months after the onset of symptoms, liver function tests were not performed. During the interval of almost three years prior to his readmission, the course was generally progressive, although some remissions were noted. Approximately four and a half years after the onset of the disease, on one occasion the cephalin flocculation test gave a positive reaction and the prothrombin time was slightly increased. The last dextrose tolerance tests showed hyperglycemia with glycosuria one hour after the administration of dextrose. Biopsy of the liver revealed the picture of chronic cirrhosis without acute features. A typical Kayser-Fleischer ring was observed. No family history of a similar disease was obtained.

Analysis revealed that the abnormal activity consisted in spontaneous irregular involuntary movements of choreatic and athetotic character on which, during active movements and during the maintenance of positions, incoordination was superimposed. The course of the disease, extending over four and a half years, was slowly progressive, with remissions.

CASE 3.—S. F., an unmarried woman aged 23, came from a family without known nervous disorders. Her past medical history was noncontributory, and her illness apparently had its onset approximately two years before her admission. At that time she became anxious and depressed. In July 1946 she was institutionalized for an acute psychosis. Under the assumption that the psychotic episode was "schizophrenic," she received ten electric shock treatments and nine insulin comas. On her return home, in October 1946, her mental status was described as "flat and lethargic."

In April 1947, ten months after the onset of her acute psychiatric illness, tremor of the left leg was noticed. This was exaggerated by activity. The symptom regressed, but a similar tremor appeared in the right upper extremity two months before her admission, in August 1947, and became progressively worse. Careful questioning failed to reveal any symptoms indicative of possible episodes of hepatic dysfunction.

Physical Examination.—The general physical condition was normal. The liver and spleen were not palpable. Neurologic examination revealed a slightly masked facies with staring eyes and infrequent blinking. Increased resistance to passive movements was noted in all extremities. No muscular weakness or sensory abnormality was found. The deep reflexes were hypoactive. Speech was monotonous. There was reduction of associated movements of the upper extremities in walking. The presence of a Kayser-Fleischer corneal ring was verified by examination with the slit lamp. Laboratory data are shown in table 3. Roentgenograms of the chest, skull and abdomen showed no pathologic condition.

Motion Picture Analysis of the Dyskinetic Phenomena.—A regular tremor of the right hand and fingers was constantly present. It consisted of alternating flexion and extension of the wrist and fingers. The pattern and the interval between the phases were always the same; only the excursions of the single movements varied to some extent. When the outstretched arms were held in the horizontal position, the pattern of alternating tremor was the same as that in the original

position "at rest." There was, however, an increase in the excursion of the single movements. During the finger to nose test the usual tremor was present in the course of the upward motion. With the finger at the nose, particularly when this position was maintained for a longer period than usual, the excursion of the alternating flexion and extension was greatly increased, and wild trembling occurred. It must be stressed that the pattern of tremor did not change; the alternating units followed one another in the same plane, and there was no swaying around in space. At times the finger was held rather quietly at the nose for a considerable length of time, until the rather sudden onset of the increased alternating activity. There was no insecurity in the Romberg position. During walking, the reduction in associated swinging of the right arm was pronounced.

After her discharge, on Aug. 20, 1947, the impairment of motor activity became progressively severer and involved all extremities. Ten days prior to readmission

TABLE 3.—*Laboratory Findings in Case 3*

	August 1947	December 1947
Complete blood count	Normal	Slight anemia
Sedimentation rate, mm./hr.	21	11
Nonprotein nitrogen, mg./100 cc.	34	29
Blood sugar, mg./100 cc.	79	76
Blood cholesterol, mg./100 cc.	164	91
Free	.....	40
Combined	.....	51
Serum protein, Gm./100 cc.	7.2	5.6
Albumin, Gm./100 cc.	4.3	3.2
Globulin, Gm./100 cc.	2.9	2.4
Serum phosphatase, Bodansky units	2.9	3.4
Inorganic phosphorus, mg./100 cc.	3.9	2.5
Bromsulphalein test	15% retention of dye after 30 min.	Less than 5% retention of dye after 30 min.
Cephalin flocculation test	+++	+++
Thymol turbidity test	.....	++
Dextrose tolerance test, mg./100 cc.		
Fasting	89	.....
½ hr.	155	.....
1 hr.	141	.....
2 hr.	97	.....
3 hr.	67	.....
4 hr.	93	.....
No sugar in urine		
Cerebrospinal fluid		
Protein, mg./100 cc.	26	.....
Cells/cu. mm.	3	.....
Colloidal gold curve	Normal	.....
Wassermann reaction	Negative	.....

(Dec. 18, 1947) she was forced to remain in bed because the "tremors" totally incapacitated her. Two days prior to readmission she was said to have become jaundiced for one day only.

On reexamination she showed hypertonicity of all muscles and a constant coarse "tremor," made worse by any excitement. There was no jaundice, and the liver and spleen were not palpable. The temperature was 101 F., and she was dehydrated and malnourished. The course was rapidly downhill, despite supportive measures and intravenous administration of sedatives, and death occurred on the ninth day. Her critical general condition did not permit the taking of motion pictures on this admission.

Necropsy (Dr. Abner Wolf).—Examination was limited to the head and removal of a specimen from the liver.

Brain: There was moderate focal degeneration in each putamen, the process extending into the lateral aspect of the globus pallidus. In addition, degenerative changes were noted in the lateral nuclei of the thalamus, in each substantia nigra,

in the inferior olivary nuclei and in the dentate nuclei. There were no clearcut abnormal changes in the cerebral cortex.

In sections through the anterior part of the corpus striatum, the caudate nucleus was seen to contain a normal number of large and small nerve cells. The wall of the ventricle in this area appeared normal. In the putamen there was widespread loss of nerve cells; in some areas this loss was so intense that the tissue was highly rarefied and finely cystic. A few large nerve cells and some smaller nerve cells had survived in these most severely affected areas. There were a concentration of oligodendroglial cells and relatively moderate astrocytosis. Occasionally large mononuclear phagocytes were present. The process extended into the lateral aspect of the globus pallidus. Except for some hyperplasia of the endothelial cells in a few blood vessels, there were no abnormalities of the vascular walls. Roughly one half of the putamen in this zone did not show abnormalities.

In a section through the left thalamus anteriorly, there were diffuse areas of rarefaction in the lateral nucleus, with diminution in the number of nerve cells. In these areas rare large mononuclear phagocytes were encountered and there was some concentration of glial cells. On the whole, astrocytosis was relatively inconspicuous.

The section through the midbrain revealed the following changes: In the lateral portion of each substantia nigra the tissue was rarefied and microcystic. In the dorsal portion of each red nucleus and the anterior cerebellar peduncle there were linear rarefied zones of microscopic size.

In the section through the upper part of the medulla, there were moderate generalized diminution in the number of nerve cells in the inferior olivary nuclei and an increase in astrocytes. In the cerebellum, some degree of the same process was seen in the dentate nucleus. There was moderate loss of Purkinje cells.

Liver: Through a small opening in the abdominal wall, palpation of the liver revealed an extremely irregular nodular right lobe. On removal of a small piece of this lobe, the surface was found to be thrown up into coarse, smooth-surfaced elevations, varying in diameter from 1 or 2 mm. to 1 cm. or more. On section, the surface of the organ was found to be crisscrossed by bands of firm pinkish gray tissue, between which there were fairly sharply outlined islands of bright yellow parenchyma.

Microscopic Examination: The lobular architecture was completely obscured, and there was an unequal division of the hepatic parenchyma by broad bands of fibrous tissue. The hepatic cells were undergoing widespread degeneration. The majority were coarsely vacuolated, and some were swollen. Some islands of the vacuolated cells which were only mildly affected showed brownish pink staining of the cytoplasm. These cells were larger than the average and had hypertrophied nuclei. In some cell clusters the hepatic cells were completely necrotic, and here there was a variable degree of infiltration of granulocytes. The connective tissue bands were moderately infiltrated with lymphocytes and contained numerous proliferating bile ducts.

Summary.—At the age of 21 the patient had a psychotic episode, for which she was treated with electric shock and insulin coma. Approximately one year after the onset of her psychiatric illness involuntary activity of the left leg developed. This was shortly followed by involvement of the other extremities. At the time of her first admission, two years after the onset of her illness, spontaneous, regular alternating tremor, increased in posture holding, was noted. No clinical evidence of hepatic disease was present, but laboratory investigation

revealed the presence of an increased sedimentation rate, a positive reaction in the cephalin flocculation test and retention of 15 per cent bromsulphalein. The presence of a Kayser-Fleischer corneal ring was verified by examination with the slit lamp.

After the patient's discharge from the hospital, the tremor increased in intensity, involved all extremities and totally incapacitated her. An episode of icterus, lasting one day, occurred before her readmission. At the time of her second admission severe spontaneous tremors were present and required constant heavy sedation. Laboratory studies at this time showed anemia, hypocholesteremia, hypoproteinemia and positive reactions in the cephalin flocculation and thymol turbidity tests.

The course was rapidly progressing and terminated fatally one and one-half years after the onset of the first dyskinetic phenomena, which indicated the presence of cerebral involvement. Before death there was laboratory evidence of a pathologic process in the liver.

The widespread lesions in the nervous system will be referred to later. The changes in the liver were those of a chronic cirrhotic process. In some areas there were acute necrotizing lesions, while in others the process was in transitional subacute stages.

CASE 4.—S. K., a married white woman aged 33, was first seen in February 1946. Two siblings were living and well. There was no family history of nervous disease.

In January 1939 the patient experienced the abrupt onset of painless jaundice associated with irritability, fatigue and slight elevation of temperature. The liver was found to be enlarged. After two weeks' hospitalization the jaundice subsided, and she returned home feeling much improved. However, within a few weeks pitting edema of the lower extremities was noted. This condition lasted a little over two years and gradually subsided. In addition, the patient noted patchy, reddish discoloration of the palms. A fluctuating positive reaction to the Wassermann test was obtained during the period of illness in 1939 and 1940. A history of syphilis was denied. The Wassermann test had given a negative reaction at the time of her marriage, eight months prior to her initial illness. Treatment for syphilis had never been received. At the time of an examination in 1940, the liver was still palpable, and edema was still present in the lower extremities.

In December 1944 the patient first noted a fine tremor of the fingers of both hands. This tremor increased with activity, making it difficult for her to hold a full glass of liquid. The tremor became worse, and by July 1945 she became unable to write. She was irritable, restless and emotionally upset. During the months immediately preceding her admission to the Neurological Institute, in February 1946, the tremor spread to involve both arms and the head. She also complained of frequent stumbling and a sensation as though she were walking down a decline. The patient had also noted impairment of memory and found herself groping for words formerly familiar.

Physical Examination (February 1946).—The patient was moderately undernourished and weighed 108 pounds (49 Kg.). The eyes were prominent. Areas of "spider" telangiectasia were noted over the chest, and discoloration of the palms was present. No edema was seen. The heart was slightly enlarged to the left, with soft systolic and diastolic murmurs in the aortic and mitral areas. The liver was palpable 2 fingerbreadths below the costal margin. The spleen was not palpable.

Neurologic Examination.—The gait was somewhat unsteady. The steps were short, and associated movements of the arms were diminished. There was a constant slight tremor of the head on walking. The patient tended to lurch to either side when walking on the toes or the heels or backward and to sway in the Romberg test.

At rest there was a fine rhythmic tremor of the head and fingers. This tremor interfered with all tests of nonequilibratory function. It was not increased with the eyes closed. Succession movements were poorly executed, but posture holding, check and rebound were normal.

Speech was slow and hesitant but not slurred or dysarthric. Examination of motor power, reflexes, sensation and the cranial nerves showed a condition within

TABLE 4.—*Laboratory Findings in Case 4*

	February 1946	February 1947
Complete blood count	Normal	Normal
Urine	Normal	Normal
Sedimentation rate, mm./hr.	2	2
Kline reaction	Negative	Positive +; negative Wassermann reaction of blood
Basal metabolic rate	−3%	.....
Serum protein, Gm./100 cc.	6.7	6.8
Albumin, Gm./100 cc.	4.3	4.2
Globulin, Gm./100 cc.	2.4	2.6
Nonprotein nitrogen, mg./100 cc.	30	36
Blood sugar, mg./100 cc.	92	87
Serum phosphatase, Bodansky units	4.0	.....
Phosphorus (inorganic), mg./100 cc.	3.1	.....
Blood cholesterol, mg./100 cc.	226 (repeated, 244)	.....
Prothrombin time	14.1 sec.	.....
Clotting time	2 min. 30 sec.	.....
Bleeding time	1 min. 45 sec.	.....
Icteric index	1	.....
Bromsulphalein test	15% retention of dye after 30 min.	.....
Cephalin flocculation test	3+; second test, negative	.....
Dextrose tolerance test, mg./100 cc.		
Fasting	93	.....
½ hr.	186	.....
1 hr.	210	.....
2 hr.	129	.....
3 hr.	67	.....
No sugar in urine		
Cerebrospinal fluid		
Protein, mg./100 cc.	27	.....
Cells/cu. mm.	1	.....
Colloidal gold curve	Normal	.....
Wassermann reaction	Negative	.....

normal limits. There was a golden yellow ring of pigmentation at the limbus of the cornea. Examination with the slit lamp showed that this was a characteristic Kayser-Fleischer ring. The laboratory data obtained at this time (February 4) and a year later are presented in table 4.

Roentgenograms of the skull, chest and abdomen revealed nothing abnormal. No esophageal varices were seen on fluoroscopic examination. The electroencephalogram was normal.

Motion Picture Analysis of Dyskinetic Phenomena.—Spontaneous involuntary activity, consisting of regular alternating movements, was present in the right forearm, hand and fingers.

When the outstretched arms were held in the horizontal position, this alternating activity was more pronounced in the right upper extremity; i. e., the excursions of the alternating movements were larger, and, in addition, slight

alternating activity of the left (contralateral) forearm and hand appeared. Analysis of slow motion pictures revealed the activity to consist of alternating pronation and supination of the forearm with extension and flexion of the fingers, the alternating cycles following one another at regular intervals.

During the finger to nose test the alternating activity was slightly increased while the hand was moved upward from the knee. There was no deviation or insecurity of the hand in moving upward from the knee to the nose.

While the finger was held at the nose, the regular alternating activity was greatly increased, resulting in severe shaking. This increase in alternating activity was more pronounced in the left hand, which showed no spontaneous activity but exhibited some activity in the horizontal position and alternating movements while the finger was held at the nose.

In the Romberg position there was some swaying. In walking, the normal associated swinging movements of the arms were diminished.

Course.—The patient was discharged with instructions to take a low fat, high protein, high carbohydrate, high vitamin diet, with supplementary cystine and choline. When readmitted on Feb. 13, 1947, she stated that since her discharge, one year before, the tremor had progressed to the point of interfering with her ability to feed or to dress herself. Intermittent slowing of speech, numbness of the left foot and difficulty in controlling movements of the left ankle were additional complaints.

Examination.—The general physical condition was unchanged from that in 1946. Accentuation of all previously noted involuntary movements was observed. A new finding at this time was impairment of strength in the left leg and ankle with questionable diminution of pain in the left foot. Her handwriting had noticeably deteriorated. Her speech was slower, with occasional stammering. She was hyperirritable, overproductive and absorbed in her illness and showed increased difficulty in remembering names. The results of laboratory studies at the time of her readmission are shown in table 4.

Summary.—At the age of 27, the patient had an attack of jaundice, with slight elevation of temperature and enlargement of the liver. Five years later involuntary motor activity appeared in the form of a tremor in one arm. The tremor increased in intensity and progressed to include both upper extremities and the head.

At the time of her first admission, one year after the onset of the tremor, spontaneous, regular alternating activity was found in the right upper extremity. This tremor was increased in rate and amplitude of excursions during active movements, particularly during the maintenance of positions. The left upper extremity showed no spontaneous tremor, but pronounced alternating activity was seen when the finger was held to the nose in the finger to nose test. No ataxia in space was observed with any motor activity.

The reaction to the cephalin flocculation test was positive on one occasion and negative on a later determination. There was retention of bromsulphalein. A Kayser-Fleischer ring was present. When she was seen again, after an interval of one year, the involuntary motor activity showed the same characteristics but had further progressed

in intensity, so that the tremor interfered with her ability to feed or dress herself.

In this case, signs of hepatic dysfunction were present five years before the onset of dyskinetic phenomena. The course of the hepatic disease was not progressive, and the nervous symptoms had progressed slightly over a period of three years.

Case 5.—S. B., a married man aged 30, was admitted in March 1947. His mother and father, one sister and a child were living and well. A maternal uncle had had a tremor of the hands and head for twenty years. A brief, transient period of jaundice had been present for one week after birth. He had been exposed to sulfur dioxide gas for some time in 1943. Immunization for yellow fever in 1941 had resulted in several cases of hepatitis in his regiment, but the patient had had no untoward symptoms himself.

On April 24, 1946 the patient was awakened at 4:30 a.m. by a severe, knifelike pain in the left flank. The pain was accentuated by movement but not by respiration. There were no other symptoms at that time. Hypodermic injection relieved the pain, but the following night a similar episode occurred. Medical examination revealed enlargement of the spleen. In May 1946 an exploratory laparotomy, with removal of a biopsy specimen of the liver, was done at another hospital. It was reported that the "liver was slightly enlarged and nodular throughout and [that] the spleen was markedly enlarged."

Microscopic Examination of the Biopsy Material.—The lobules were greatly enlarged and nodular. Their cells were frequently large and bizarre. Separating the lobules were bands of fibrous tissue, infiltrated with many inflammatory cells, chiefly lymphocytes and occasionally eosinophilic granulocytes. These septums did not always correspond with the portal areas. The capsule of the liver was thickened and infiltrated with the same variety of cells. There was little evidence of active formation of liver cells. A moderate number of liver cells contained bile pigment. It was concluded that the large nodular liver with scarring between the nodules somewhat suggested that the organ had survived an attack of subacute yellow atrophy and the surviving lobules had undergone hypertrophic enlargement. The spleen showed some evidence of congestion but no fibrosis.

Course.—After operation, while on a high vitamin, high protein diet with supplementary choline and methionine, the patient began to feel weak and nervous. The gradual onset of coarse tremors was noted. This tremor was made worse by movement. Speech became slurred and rather nasal, but this symptom subsided within a few months.

In the period from operation until his admission, in March 1947, the neurologic status progressed little except for the additional symptoms of easy fatigability and irritability. However, the spleen progressively enlarged. There were an episode of hematemesis and several episodes of tarry stools.

Examination.—On admission the patient appeared well developed and exhibited an irregular, coarse tremor of all extremities. This seriously interfered with skilled volitional acts. A Kayser-Fleischer ring was noted bilaterally. Results of the rest of the neurologic examination were not remarkable. The spleen was palpable and slightly tender. The liver was not palpable, and liver dulness was absent. One dilated vein was noted in the left lower quadrant of the abdomen. Laboratory data for various investigations are shown in table 5.

The stools gave negative reactions for blood. Roentgenograms of the chest and heart showed a normal condition. An electrocardiogram was normal. Venous

pressure (arm) was 95 mm. of saline solution. Fluoroscopic examination revealed esophageal varices.

Motion Picture Analysis.—Spontaneous activity was not observed while the patient held his extremities relaxed and "at rest." Only slight alternating activity with small excursions appeared when the arms were held outstretched in the horizontal position.

In the finger to nose test, no involuntary activity appeared while the hand was moved to the nose. But when the hand was held to the nose for a considerable length of time, there appeared a strong involuntary activity consisting of alternating flexion and extension of the hand, pronation and supination of the forearm and internal and external rotation of the arm in the shoulder. The excursions were wide, but, at least on the right, the pattern of the alternating cycles of each part

TABLE 5.—*Laboratory Findings in Case 5*

	December 1946	February 1947	March 1947	September 1947
Cephalin flocculation test	++++	++++	++++	++++
Urea nitrogen, mg./100 cc.	8.5	....	16	18
Calcium, mg./100 cc.	9.5	....	10.2	....
Phosphorus (inorganic), mg./100 cc.	3.1	....	3.5	....
Serum phosphatase, Bodansky units	5.9	....	3.5	....
Icteric index	11	3	....	....
Serum protein, Gm./100 cc.	8.3	....	7.7	6.0
Albumin, Gm./100 cc.	....	....	3.8	3.8
Globulin, Gm./100 cc.	....	....	3.9	2.2
Bromsulphalein test	No retention after 30 min.	....	15% retention after 30 min.	....
Complete blood count	....	Anemia	Anemia	....
Erythrocyte sedimentation rate, mm./hr.	....	....	28	....
Blood sugar, mg./100 cc.	....	....	85	....
Dextrose tolerance test, mg./100 cc.				
Fasting	....	....	81	....
½ hr.	....	....	172	....
1 hr.	....	....	183 (urine +)	....
2 hr.	....	....	180 (urine +)	....
3 hr.	....	....	121 (urine +)	....
Blood cholesterol, mg./100 cc.	....	....	210	....
Prothrombin time	....	....	....	18.8 sec.
Cerebrospinal fluid				
Protein, mg./100 cc.	....	....	34	....
Cells/cu. mm.	....	....	3	....
Wassermann reaction	....	....	Negative	....

of the extremity was completely regular. Agonist and antagonist action produced movements in the same plane of space. On the left, it was not quite clear whether or not, with these regular alternating cycles there was interposed a swaying in space with instability in the various joints. Sometimes the patient succeeded in interrupting the severe shaking for a short time; then the tremor started again and became increasingly severe.

The finger to finger test resulted in violent activity when the forefingers were held in the horizontal position before the chest. Analysis of slow motion pictures revealed that the pattern of the involuntary movements of the right upper extremity was regular and consisted of alternating units. On the left side, however, in addition to the alternating activity, shifting from one special plane to another was definitely observed. Parts of the limb swayed in the various joints without any regularity. During prolonged attempts to hold the posture, the alternating activity spread to the head and both lower extremities. The Romberg test showed no abnormalities. The gait was normal.

After splenorenal anastomosis with splenectomy, atelectasis of the lower lobe of the left lung developed, followed by intra-abdominal hemorrhage, bleeding from esophageal varices and jaundice. The patient died on the sixth postoperative day. Permission for autopsy was refused.

Summary.—At the age of 29, the patient experienced the acute onset of signs and symptoms, with laboratory findings, which pointed to subacute disease of the liver. A laparotomy was performed, and biopsy of the liver showed evidence of subacute yellow atrophy. After this the gradual onset of tremor was noted. However, hepatic symptoms and enlargement of the spleen continued to predominate. One episode of hematemesis and several episodes of tarry stools pointed to the development of esophageal varices. Laboratory studies made at intervals during the course of the disease revealed persistently positive reactions to the cephalin flocculation test, anemia, leukopenia, thrombocytopenia and increased globulin-protein fractions. On one occasion there was significant retention of bromsulphalein. In addition to these signs, a characteristic Kayser-Fleischer ring was present bilaterally.

Spontaneous abnormal motor activity was not present. Alternating activity appeared during posture-holding situations. The pattern of the alternating cycles was entirely regular in the right upper extremity. On the left, some discoordination was present, in addition to the regular alternating activity.

The course of the disease in this patient rapidly progressed. Hepatic symptoms were always severer than the signs of involvement of the nervous system. One and one-half years after the onset of the disease, hematemesis and tarry stools occurred as the result of esophageal varices, and the patient died of hepatic insufficiency after splenorenal anastomosis had been performed.

Case 6.—G. V., a Negro aged 26, unmarried, was admitted to the Neurological Institute on March 8, 1948. The patient had been born in Georgia; both the paternal and the maternal great-grandfathers were said to have been "white Americans."

The patient had measles and chickenpox as a child and "flu" in 1941. At that time the patient had severe weakness and malaise with pain in the chest and cough. No gastrointestinal symptoms were noted. Of possible significance was the spontaneous report of the patient that his mother noticed a yellow tinge to his eyes. He was ill for six weeks but was not hospitalized. After this episode, he felt well until the onset of the present illness, in July 1947. At that time he had "weak knees" and noted that he sometimes "veered to the right" while walking. No tremor or other symptoms were present at that time.

In October 1947, after having consumed ⅓ pint (158 cc.) of whisky with his dinner, followed by two more drinks, he noted that his right hand shook so that he spilled the drink. He was able to pick up a glass but not to carry it to his mouth without spilling its contents. He stated that he felt perfectly well in every other respect and did not notice any tremor except in the right hand. Questioning brought out that about this time (October 1947) there had been some change in speech. He denied the presence of all other symptoms and stated the belief that his disability had not progressed in the eight months prior to admission.

Examination.—The general physical condition was entirely normal. The liver and spleen were not enlarged. There were a mild degree of dysarthria and slight euphoria. He tended to veer to the right in walking and occasionally showed a minimal tremor of the head. Inspection and examination with the slit lamp revealed a typical advanced Kayser-Fleischer ring bilaterally—"a wide band of golden pigment on the posterior surface of the cornea [actually at the level of Descemet's membrane], continuous with the limbus." The motor phenomena will be described in the "Motion Picture Analysis." Laboratory data are shown in table 6.

Roentgenograms of the skull and chest revealed a normal condition, as did an electroencephalogram. The visual fields and audiometric findings were normal.

Motion Picture Analysis of the Dyskinetic Phenomena.—There was no spontaneous hyperkinesis. The posture was somewhat stiff and the facies masklike. When the outstretched upper extremities were brought up to the horizontal position in front of the chest, neither insecurity nor tremor was observed. Only a fine

TABLE 6.—*Laboratory Data in Case 6*

Complete blood count	Normal
Urine	Normal
Nonprotein nitrogen, mg./100 cc.	25
Erythrocyte sedimentation rate	4 mm./hr.
Kline reaction	Negative
Cephalin flocculation test	Negative
Thymol turbidity test	Negative
Prothrombin time	16.9 sec.
Serum bilirubin, mg./100 cc.	0.2
Bromsulphalein test	Less than 5% retention after 30 min.
Phosphorus (inorganic), mg/100 cc.	3.5
Serum phosphatase, Bodansky units	2.6
Serum protein, Gm./100 cc.	7.5
Albumin, Gm./100 cc.	4.8
Globulin, Gm./100 cc.	2.7
Cerebrospinal fluid	
Protein, mg./100 cc.	50
Cells/cu. mm.	2
Colloidal gold curve	Normal
Wassermann reaction	Negative

regular tremor of both hands and fingers was observed when the position was maintained for a considerable length of time.

In the performance of the finger to nose test no tremor was present during the upward movement. The outstretched fingers of the right hand were first held quietly to the nose; then a rather coarse alternating tremor of the forearm set in. This consisted of alternating upward and downward motion occurring simultaneously with supination and pronation of the forearm. This pattern of movements of the right arm was combined with flexion and extension at the wrist and fingers. The left upper extremity showed a slightly different pattern when the finger was held to the nose. The alternating movements consisted of flexion and extension of the forearm alone. In all instances, the tremor was regular and appeared in the same plane of space, and there was no incoordination.

Regular alternating tremor also appeared when the outstretched upper extremities were raised above the head. The excursions of the regular alternating units in the left upper extremity were larger than those in the right.

Summary.—The patient experienced a fairly abrupt onset of motor symptoms at the age of 26. During the period of observation, eight months after the first symptoms, regular alternating tremor in both

upper extremities was present during prolonged maintenance of certain postures. There was no discoordination and no tremor "at rest."

Definite evidence of hepatic disease could not be deduced from either the history or the laboratory examination. The "yellow tinge" reported during a febrile episode six years prior to his motor symptoms was too unreliable for the assumption of the presence of hepatic disease at that time. There was no family history of similar disease. A Kayser-Fleischer ring was present.

The course of the disease during the short period of observation (eight months) was static and nonprogressive.

CASE 7.—F. G., a white man aged 39, was admitted in March 1947 for investigation of abnormal involuntary movements first noted by him in 1927, at the age of 19. Questioning failed to reveal any history of familial nervous disease. A review of the personal medical history revealed only frequent episodes of constipation, without evidence of hepatic disease.

In 1927 the patient first noted that it had become necessary to overflex his right wrist in order to overcome a slight tremor of his hand which interfered with writing. At about the same time he was told that he was taking "a short step" with the right foot.

By 1930 a coarse tremor of the right hand, greatly increased by effort, began to interfere with his activities. Later the same year the right knee began to give way in walking, and the right ankle would "turn over" easily. At this time a limp was manifest.

Involuntary flexion movements of the right thigh and inversion spasm of the right foot began to be noted by 1932, five years after the onset of his illness, and have persisted to the time of writing. Between 1930 and 1935 the patient lost about 20 pounds (9.1 Kg.) and was constantly tired and upset. He worried greatly about the slow, but steady, march of his symptoms. Despite this, he learned to type and set a record for speed in mail sorting. In addition to the steady progression of tremor and involuntary movements of the leg and thigh, the patient noted slurring of speech in 1942. The latter complaint was aggravated by tension, excitement or the desire to speak rapidly. From 1942 until the time of admission to the Neurological Institute, in March 1947, he regained weight. On multivitamin therapy, he felt better generally but stated that the symptoms described had continued to progress.

Examination.—The general physical condition was normal. Neither the liver nor the spleen was palpable. Neurologic examination revealed slight slurring of speech. Examination of the reflexes and the sensory and cranial nerves showed nothing remarkable. Motor strength was unimpaired. Abnormal involuntary motor activity was seen on the right side only. Examination with the slit lamp revealed peripheral corneal infiltration involving the interstitial tissues with definite demarcation, which, while not the typical Kayser-Fleischer phenomenon, impressed the examiner as a "Kayser-Fleischer ring in its early stages."

Roentgenograms of the skull and chest revealed nothing abnormal. Arthritic changes were noted in both the distal tarsal and the tarsometatarsal articulations. No roentgenologic evidence of enlargement of the liver was seen. The splenic shadow was questionably large but did not extend below the costal margin. The electroencephalogram was normal.

Motion Picture Analysis of the Dyskinetic Phenomena.—The spontaneous involuntary activity was confined to the right foot. At irregular intervals inward

rotation set in and was maintained for a considerable length of time. This phenomenon was particularly frequent in walking when the right lower extremity was swung forward. Inward rotation was not observed during the weight-bearing phase. The normal associated swinging movements of the right arm during walking were absent, and the right hand presented a stiff posture with dorsiflexion of the wrist. The Romberg test showed nothing abnormal.

When the patient moved his arms upward into the horizontal position, no involuntary activity was noticed during the upward excursion. When the outstretched upper extemities were held in the horizontal position, regular alternating supination and pronation of the right forearm were observed.

During the performance of the finger to nose test, the upward movement from the knee to the nose was straight and without interference. However, on the right side, when the finger was held to the nose for some time, regular alternating activity of the hand and forearm started, consisting of flexion and extension of the fingers and pronation and supination of the forearm. Superimposed on the alter-

TABLE 7.—*Laboratory Findings in Case 7*

Complete blood count	Normal
Urine	Normal
Nonprotein nitrogen, mg./100 cc.	40
Erythrocyte sedimentation rate	2 mm./hr.
Kline reaction	Negative
Blood sugar, mg./100 cc.	88
Blood cholesterol, mg./100 cc.	236
Blood bilirubin, mg./100 cc.	0.2
Serum phosphatase, Bodansky units	3.6
Phosphorus (inorganic), mg./100 cc.	2.6
Serum protein, Gm./100 cc.	6.3
Albumin, Gm./100 cc.	4.5
Globulin, Gm./100 cc.	1.8
Cephalin flocculation test	Negative
Bromsulphalein test	Less than 5% retention after 30 min.
Cerebrospinal fluid	
Protein, mg./100 cc.	43
Cells/cu. mm.	2
Colloidal gold curve	Normal
Wassermann reaction	Negative

nating cycles, and regularly following each other in the same plane of space, there was a slight swaying of the right forearm and arm in various directions of space. There was no abnormal activity or insecurity in the movements and postures of the left upper extremity.

When the outstretched finger of the right hand was led and held to the shoulder, the involuntary activity was reduced as soon as the elbow was held stiff or pressed against the chest.

Summary.—In this case involuntary motor activity started at the age of 19 and in slow progression affected the upper and lower extremities on the right side only. At the time of the patient's admission, twenty years after the onset of the first symptoms, spontaneous dystonic movements of the right foot and some posturing of the right hand were observed. Alternating activity of the right upper extremity appeared only when certain positions were maintained for some length of time. Additional ataxic phenomena in this extremity were slight.

There was neither clinical nor laboratory evidence of impaired hepatic function. A peripheral corneal infiltration was considered suggestive of a Kayser-Fleischer ring. In the absence of any disturbance of hepatic function and the doubtful presence of a corneal color ring, the diagnosis in this case must be kept open until confirmation can be provided by investigation of the pathologic process in the brain and liver.

ANALYSIS OF DYSKINETIC PHENOMENA

In all cases of hepatolenticular degeneration reported in the literature, dyskinetic phenomena were the predominant neurologic symptoms. Involvement of the nervous system was deduced from the appearance of abnormal involuntary motor activity, disturbances of postural fixation and impairment of volitional movements or acts.

TABLE 8.—*Significant Features of Dyskinetic Phenomena in 7 Cases of Hepatolenticular Degeneration*

Case No.	Spontaneous Activity	Maintenance of Positions	Performance of Active Movements
1	None	Severe discoordination	Slight discoordination
2	Chorea	Chorea; severe discoordination	Chorea
3	Alternating tremor of right hand	Severe alternating tremor of right hand and forearm	Severe alternating tremor of right and left hand
4	Alternating tremor of right arm and hand	Severe alternating tremor of right and left hand	Slightly increased alternating tremor of right and left hand
5	None	Severe alternating tremor of right and left hand; discoordination of left side	None
6	None	Alternating tremor, right and left hand	None
7	Dystonic movement of the right foot	Alternating tremor and discoordination of right side	None

In the material presented, the pattern of the motor disturbance was analyzed in various situations. The presence or absence of spontaneous abnormal motor activity was recorded while the patient was "at rest" and apparently relaxed in the standing, sitting or supine position. The maintenance of positions and the performance of active movements were tested when the patient raised his outstretched arms to the horizontal position or when he performed the finger to nose test. The end position had to be maintained for a few minutes. Characteristic disturbances were found in these situations.

Spontaneous Regular Alternating Tremor "at Rest" (cases 3 and 4).—Slow motion pictures demonstrated the sequence of units consisting of agonist and antagonist activity, which followed each other at regular intervals. The pattern of alternating movements was always stereotyped, and the alternating cycles occurred in the same plane of

space. Only the speed and extent of the movements varied in the same case.

Spontaneous Irregular Involuntary Activity (cases 2 and 7).—Isolated simple movements of different parts of the limbs or trunk appeared at irregular intervals. They were regarded as choreatic movements when their course was even, uninterrupted and relatively fast (case 2) or as athetotic and dystonic movements when their course was slow and stiff and intermediate or end positions were sustained (case 7).

Absence of Spontaneous Abnormal Involuntary Activity (cases 1, 5 and 6).—Akinetic phenomena, such as loss of spontaneity, slowness of active movements, reduction of associated movements and the specific waxy resistance to passive movements (rigidity), were not pronounced in this series but have frequently been described in previous reports.

Impairment of Maintenance of Positions.—This was severe in all cases. Slow motion picture analysis revealed various dyskinetic patterns. In case 1 no spontaneous activity was present "at rest." During maintenance of position, the whole limb, as well as its parts, began to sway in space. The direction of the movements varied constantly. The variations in the pattern of movements of the arm, forearm and hand were determined only by the mechanics of the joints in which the parts of the limb moved. The ball and socket arrangement of the shoulder joint, for instance, makes possible a wide range of circling and rolling movements of the arm in all planes of space, whereas the ellipsoid joint of the wrist permits fewer variations of motion. The mechanics of the elbow joint allows a still more limited range of motility; extension and flexion of the forearm may be combined with pronation and supination. Instability of the limb was somewhat diminished and the swaying was less pronounced when one or the other joint of the extremity was held by voluntary fixation. When, for instance, the elbow joint was voluntarily splinted while the upper extremities were held in the horizontal position in front of the chest, the instability affected predominantly the hand and fingers. As soon as the elbow was bent, and the active stabilization thus released, the swaying of all parts of the extremities became again more pronounced.

This disturbance of postural fixation was previously termed "static intentional ataxia."[4] It is produced by lack of coordination ("asynergia" of Babinski) of wider groups of muscles which normally secure joint fixation.

The disorder during maintenance of positions in cases 3 and 4 presented completely different features. Here, regular alternating tremor already present in the relaxed position, "at rest," appeared in increased intensity when positions had to be maintained over a considerable length of time. The pattern of the tremor remained stereotyped,

and the cycles of antagonist movements ran in the same plane of space. Only the speed and amplitude of the single movements were larger in this situation than they were in the position of the extremity "at rest."

In case 4 there was no alternating tremor in the left upper extremity while it was in the rest position, but the tremor became pronounced during the maintenance of postural fixation. This remarkable appearance of alternating tremor exclusively during the maintenance of positions was also observed in cases 5 and 6. In the latter, the upper extremity did not show tremor "at rest"; only the right foot was affected by dystonic activity. In case 5 spontaneous activity was not present at all.

Motion picture analysis thus showed that two principally different mechanisms were responsible for the dyskinetic phenomena during the maintenance of positions, namely, (1) discoordination and (2) appearance of regular alternating tremor or increase of spontaneously present alternating tremor. These characteristic features may be in pure form in a given case, or they may be present simultaneously, as in cases 5 and 6. Here, regular alternating units were present, but, in addition, different parts of the limb swayed in various planes of space. The mechanisms of this complicated pattern, usually designated as *Flügelschlagen,* or "wing beating," can be clearly differentiated by the slow motion picture technic.

Dyskinetic Phenomena During Performance of Active Movements.—The same dyskinetic phenomena were observed in the carrying out of active movements but were much less pronounced than during the maintenance of position. In case 1 only slight discoordination was apparent while the arm was lifted to the horizontal position or the hand was raised from the knee to the nose. However, when the patient was asked to drink from a glass of water and his arm stopped in an intermediate position, he was not able to stabilize this position. His hand with the glass then showed extreme swaying about. In cases 3 and 4, with spontaneous alternating tremor, the tremor persisted during active motility and was slightly increased in intensity. In cases 5, 6 and 7, with severe alternating tremor and some discoordination during the maintenance of positions, relatively fast active movements were not impaired.

The significant features of the dyskinetic phenomena in this series of cases of hepatolenticular degeneration are summarized in table 1.

1. Spontaneous abnormal involuntary activity may be absent or, if present, may show the characteristics of regular alternating tremor or of choreatic, athetotic or dystonic movements.

2. The maintenance of position was impaired in all cases. Discoordination (static intentional ataxia) was present in pure form in 1 case. In other cases spontaneously present alternating tremor was increased in intensity, or alternating tremor, not present "at rest," appeared during

prolonged maintenance of positions. In a third group of cases both discoordination and alternating tremor were found in this situation.

3. During the performance of fast active movements, impairment by discoordination or alternating tremor was present but was less severe than during the maintenance of positions.

Comment.—In 1904 Holmes,[5] in his description of various forms of tremor in organic lesions, made the following statement, which is still valid to some extent.

> A full review of the literature is very difficult . . . as . . . there has hitherto been but little attempt to distinguish between or classify the various forms of disorder of movements. . . . In the large proportion of cases there is no accurate description of the clinical observation, many of the authors being contented with describing what they observed merely by conventional terms or even in unconventional nomenclature.

Holmes defined tremor at that time as "a clinical phenomenon consisting in the involuntary oscillation of any part of the body around any plane, such oscillation being either regular or irregular in rate and in amplitude and due to the alternate action of groups of muscles and their antagonists." The classic description of cerebellar discoordination was given by Holmes[6] (1939) in his Hughlings Jackson Lecture. In compound movements—movements which involve change of posture at two or more joints—"irregularities in rate, force and range of each component of the movement complicate the execution of synchronous or successive components." Most pronounced is "the defective postural fixation of the moving limb, particularly at the proximal joints where the weight and momentum of the moving limb particularly require steadying by tonic contraction of the muscles around them." There is "lack of plasticity," by which the muscles adapt themselves to changing conditions. "The result is that the moving limb is liable to sway about . . . instead of conforming accurately to the posture of displacement required of it in the action."

The differentiation of these principally different phenomena has only rarely been respected in the description and analysis of the dyskinetic phenomena of hepatolenticular degeneration. Wilson,[1] in his original monographic description (1912) as well as in the chapter on progressive lenticular degeneration in his textbook[7] (1940), stressed that the regular rhythmic alternating tremor occurs at rest but is heightened by action. "In this respect, it is not quite comparable to

5. Holmes, G.: On Certain Tremors in Organic Cerebral Lesions, Brain **27**:327, 1904.

6. Holmes, G.: The Cerebellum of Man, Brain **112**:1, 1939.

7. Wilson, S. A. K.: Neurology, Baltimore, William Wood & Company, 1940, vol. 2.

that of paralysis agitans." Westphal [2] (1883) elaborated on the occurrence of tremor in connection with voluntary movements: "It is only minimal and occurs but occasionally without voluntary impulses, and is increased to severe shaking with stronger activity." Strümpell [3a] (1898) observed in his cases of so-called pseudosclerosis "peculiar rhythmic shaking phenomena" which occur "solely with intentional movements. . . . As soon as the patient raises the outstretched arms, rhythmic tremor appears in the whole arm. It increases in severity and can best be compared to certain swimming movements or to wing beating (*Flügelschlagen*) of young, unskilful birds." Strümpell added that "oscillatory tremor" is not always the significant symptom. Sometimes "tremor appears in the common, irregular form of intentional tremor or intentional ataxia, present chiefly in cases of genuine multiple sclerosis." In the recent comprehensive monograph on "Diseases of the Basal Ganglia," Denny-Brown [8] stated that the tremor of hepatolenticular degeneration is rhythmic and is irregular in amplitude only in early development. Its absence in complete repose and its increase on movement are, in his opinion, further peculiarities. In addition, he observed that the "tremor is mildly increased by movement but greatly increased by certain postures." Homburger and Kozol [9] also described the tremor in this disease as being "brought out or exaggerated by sustained muscular tension rather than by movement."

With reference to the original differentiation of the "Wilson type" and the "Westphal pseudosclerosis type" of hepatolenticular degeneration, Josephy [10] attempted to separate the parkinsonian tremor of the former from tremor increased by intentional activity, similar to that in multiple sclerosis, in the latter.

Hunt's [11] interpretation of complicated "combined" forms of organic tremor deserves special attention. Holmes had described focal lesions in the midbrain with the occurrence of regular alternating tremor complicated by wide irregularities of the intention tremor type. He ascribed this peculiar pattern to lesions of the cerebellorubrospinal system. Hunt postulated the "striocerebellar" form of tremor. It combines the features of the rhythmic tremor "at rest" and of a disturbance of postural control, with resulting "atactiform" tremor. Unfortunately, in the verbal description of his case of hepatolenticular degeneration the

8. Denny-Brown, D.: Diseases of the Basal Ganglia and Subthalamic Nuclei, New York, Oxford University Press, 1946.

9. Homburger, F., and Kozol, H. L.: Hepatolenticular Degeneration, J. A. M. A. **130**:6 (Jan. 5) 1946.

10. Josephy, H.: Degeneratio hepato-lenticularis, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 16.

11. Hunt, J. R.: The Strio-Cerebellar Tremor: A Study of the Nature and Localization of the Combined Form of Organic Tremor, Arch. Neurol. & Psychiat. **8**:664 (Dec.) 1922.

components of the dyskinetic pattern are not clear. However, regular alternating tremor, in addition to discoordination, seems to have been present in certain positions in which the "ataxic shaking assumed a more or less rhythmic character." Hunt concluded that in these complicated dyskinetic patterns the influence of the cerebellar lesions supervenes in some cases and the influence of the striatal lesions dominates the resulting clinical picture in others.

The clinical analysis of the dyskinetic phenomena in our series of cases of hepatolenticular degeneration points to the occurrence of cerebellar disturbances in all instances. Several variations have to be considered. Discoordination like that caused by lesions of the cerebellum or its pathways may be exclusively present without any spontaneous abnormal involuntary activity, such as that produced by striatal lesions. Or, ataxia, particularly during the maintenance of positions, may be combined with abnormal involuntary activity previously present "at rest." This complicated hyperkinetic pattern can be explained by the simultaneous involvement of striatal and cerebellar structures.

In some observations the occurrence of regular alternating cycles, which could not be differentiated from typical parkinsonian tremor, in the absence of discoordination might support the assumption of a purely striatal disturbance. However, this regular alternating tremor in the cases of hepatolenticular degeneration showed characteristic differences from the tremor of parkinsonism. In some instances it appeared only during the maintenance of positions and during active movements and was not present when the limbs were "at rest." In other instances the intensity of the alternating tremor, its amplitude and speed, was increased during the maintenance of positions and during active movements, whereas parkinsonian tremor is abolished, or at least decreased in intensity, during activity of the muscles which participate in the alternating cycles. Thus, striatal disturbances—in the form of spontaneous alternating tremor—appear or are increased in severity in motor situations when coordinatory stabilization of postures and coordinatory guidance of movements are a particularly necessary constituent of the performance. Additional cerebellar disturbance seems to promote the appearance and intensity of striatal disorders in situations which afford a particular degree of coordination.

As it is not known where the integration of striatal and cerebellar function takes place, lesions of the cerebellum, including those of the dentate nucleus, as well as lesions of the ascending fibers in the brachium conjunctivum, of the red nucleus or even of connections up to the thalamus, might produce the described discoordination of cerebellar character. Similar irregular forms of "tremor" have been frequently observed in association with lesions of the superior cerebellar peduncles, but the information thus far available does not permit a more detailed localization.

The pathologic process of hepatolenticular degeneration is not confined to the lenticular nuclei, as Wilson [1] assumed in his first description. Rotter,[12] Spielmeyer,[13] von Lehoczky,[14] Miskolczy[15] and others, including Wilson [7] in his last communication, called particular attention to lesions in the cerebellum. These lesions have the same pathologic characteristics as those in the ganglia of the forebrain. The question of the correlation of the various clinical pictures of hepatolenticular degeneration with the localization and distribution of the pathologic process in the structures of the brain stem remains to be solved.

CLINICAL FINDINGS AND LABORATORY DATA IN RELATION TO DAMAGE TO THE LIVER

There was no doubt of the clinical diagnosis of hepatolenticular degeneration in cases 1 to 6. A typical Kayser-Fleischer ring was

TABLE 9.—*Clinical and Laboratory Evidence of Damage to the Liver*

Case No.	Evidence of Hepatic Impairment: Clinical	Evidence of Hepatic Impairment: Laboratory	Time of Observation	Course
1	—	—	5 yr.	Static
2	—	+	4½ yr.	Slight irregular progression, with remissions
3	+	+	1½ yr.	Rapid course
4	+	+	Liver: 8 yr. Neurologic signs: 3 yr.	Slight progression in neurologic condition; no progression of hepatic disease
5	+	+	1½ yr.	Severe progression in hepatic disease, after splenorenal anastomosis
6	—	—	8 mo.	Static (early case)
7	—	—	20 yr.	Slow progression; doubtful diagnosis

present, in addition to the characteristic neurologic symptoms, in particular the dyskinetic phenomena. The clinical picture in case 7 was atypical in some respects. The dyskinetic phenomena were only unilateral, and the marginal corneal pigmentation was only "suggestive" of a Kayser-Fleischer ring.

Laboratory tests of hepatic function revealed an abnormal condition in 4 of 7 cases (table 9). The cephalin flocculation test gave a 4 plus

12. Rotter, R.: Beitrag zur Histopathologie und Pathogenese der Wilson-Pseudosclerose Gruppe, Ztschr. f. d. ges. Neurol. & Psychiat. **111**:159, 1927.

13. Spielmeyer, W.: Die histopathologische Zusammengehörigkeit der Wilsonsche Krankheit und Pseudosclerose, Ztschr. f. d. ges. Neurol. & Psychiat. **57**:312, 1920.

14. von Lehoczky, T.: Zur Anatomie und Klinik der Wilson-Pseudosclerose Gruppe, Arch. f. Psychiat. **95**:481, 1931.

15. Miskolczy, D.: Wilsonsche Krankheit und Kleinhirn, Arch. f. Psychiat. **97**:27, 1932.

reaction in all these cases. The next most frequent abnormality was the reduction of serum albumin, usually with a reduction in the total serum protein. In cases 3, 4 and 5 the bromsulphalein test showed retention of 15 per cent of the dye thirty minutes after injection. The value for alkaline serum phosphatase was above the normal of 4 Bodansky units in only 1 case (5.9 units); repeated examinations at a later date showed a value within normal limits (3.5 units). The blood cholesterol was down to 91 mg. per hundred cubic centimeters in 1 case, whereas the determination in other cases showed normal values. The blood sedimentation rate was high in 3 cases. Thus, in the present series, the positive reaction in the cephalin flocculation test and the reduction of serum albumin were the pathologic changes found most frequently.

Aside from the laboratory findings, subjective complaints and objective signs suggestive of hepatic disease were present in 4 cases (3, 4, 5 and 6). In case 2, with positive laboratory evidence, additional clinical signs of impaired hepatic function were never apparent during the almost five years after the onset of the first neurologic symptoms. In case 6 the patient described an illness of six weeks' duration, with a yellow tinge in both eyes, which occurred six years before the onset of the first neurologic symptoms. Laboratory studies, performed nine months after the onset of the dyskinetic symptoms had developed, did not reveal any signs of damage to the liver. In case 3 an acute psychosis developed ten months before the onset of dyskinetic phenomena. During the further course of the disease, when the dyskinesia had already incapacitated the patient, she was jaundiced for a short time only. In the following week rapid physical deterioration, with hepatic insufficiency and signs of cholemia, developed and the patient succumbed to this condition. The disease in case 4 had its onset with painless jaundice, with slight elevation of temperature and general fatigue. The liver was still enlarged when, five years later, the nervous symptoms appeared. In case 5 the signs of pathologic involvement of the liver were predominant during the whole course of the disease. After the acute onset of abdominal pain, a laparotomy was performed, and an enlarged nodular cirrhotic liver and enlarged spleen were found. After this operation dyskinetic phenomena developed gradually. However, the deterioration of the general physical condition was much more pronounced than the progression of the nervous symptoms. Episodes of hematemesis and of tarry stools were due to the esophageal varices, which were found on fluoroscopic examination. Six days after a splenorenal anastomosis, the patient died of intra-abdominal hemorrhage, originating in bleeding esophageal varices. Neither clinical nor laboratory evidence of hepatic impairment was reported in 2 cases (cases 1 and 7) during the duration of the disease (five and twenty years, respectively).

The course of the illness in 3 cases (of the 6 cases with an undoubted diagnosis of hepatolenticular degeneration) extended over five, four and a half and eight years, respectively (table 2). Progression of the nervous symptoms was slight after the handicap had reached a certain peak. In 1 of these 3 cases with a long course (case 1) there was neither clinical nor laboratory evidence of hepatic disease for the five years of observation after the onset of the first symptoms. In case 2 only laboratory evidence of disturbed hepatic function could be found. The course of the nervous disorder was only slightly progressive, and remissions were observed during the four and one-half years of observation. Although clinical and laboratory evidence was present for eight years in case 4, the dyskinetic phenomena, which appeared only during the last three years of the disease, progressed but slightly, and the impairment of the liver never became severe. Case 6, without clinical and laboratory evidence of hepatic impairment, was observed for only eight months. Up to that time the course of the disease had been rather static. The course in 2 other cases (cases 3 and 5) was rapidly progressive. The patients died after an illness of only one and one-half years' duration. Obvious clinical and laboratory evidence of severe damage to the liver was present in both cases.

In correlating the course of the disease with the severity of the hepatic damage in this small series of observations, one can differentiate two types of reactions in hepatolenticular degeneration. In one type the prolonged, chronic course, without serious progression, was associated with no clinically apparent damage to the liver or with only slightly progressive hepatic impairment. The course in the 2 cases representing the other type was rapidly progressive, with a duration of only one and one-half years before death. In these cases clinical signs and symptoms of damage to the liver were most obvious, and the hepatic disease progressed rapidly. The extent and the severity of the clinically recognizable damage to the liver were therefore correlated with the course and progression of the disease.

It appears from these observations that the chronicity or acuteness of the hepatic disturbance is a pertinent characteristic in a given case. Further observations on the extent of damage to the liver in various phases of the disease might, however, reveal evidence that hepatic failure is only an episode during a prolonged course. Various possibilities must be considered. Hepatic failure leading to death may occur early in the disease or later, after a prolonged neurologic course. Furthermore, hepatic failure may be compensated, and, after the patient has recovered from the acute hepatic disturbance, a long neurologic course may be observed.

VARIETIES OF CIRRHOSIS OF THE LIVER IN HEPATOLENTICULAR DEGENERATION

Microscopic examination of the liver could be performed in 3 cases. In 2 instances the material was obtained by biopsy; in case 3 an autopsy was performed. In all 3 cases the gross appearance of the liver showed the characteristics of cirrhosis of the liver. The volume was reduced and the surface was nodular, with the hobnail appearance. There was, however, a definite difference between the microscopic features of case 2, with a prolonged chronic course over four and one-half years, and those of cases 3 and 5, with rapid progression and significant impairment of hepatic function. In case 2, connective tissue proliferation was prevalent, and coarse bands surrounded irregular groups of hepatic cells. This evidence of a more chronic process was also present in the 2 other cases. In addition, signs of acute degeneration with acute necrosis of hepatic cells was present. There was a varying degree of granulocytic infiltration. These features are those of a rather acute process which is superimposed on the chronic cirrhotic degeneration.

Lack of knowledge of etiologic factors responsible for the production of the disease process in the liver, as well as in the central nervous system, does not permit speculations as to the reason that in some instances a chronic process develops and in others the pathologic picture resembles subacute yellow atrophy of the liver.

In the pathologic investigation of the 3 cases in our series, the previously mentioned correlation of chronicity of the process in the liver and a slowly progressing, prolonged course of hepatolenticular degeneration and of acuteness of damage to the liver and rapid progression of the disease was found.

PATHOLOGIC CHANGES IN THE BRAIN IN "ORDINARY ACQUIRED" DISEASE OF THE LIVER IN MEN AND ANIMALS

The possibility of causative relation of hepatic disease to structural changes in the brain stem in hepatolenticular degeneration has been frequently discussed in the past, and theories referring to the pathogenesis of this disease have been offered. The crucial question whether in the "ordinary acquired" diseases of the liver changes in the central nervous system are the same, or at least similar, to those associated with hepatolenticular degeneration was discussed in detail by Stadtler [16] and followed up by Waggoner and Malamud [17] after Crandall and Weil [18]

16. Stadtler, H.: Histopathologische Untersuchungen zur Frage der Beziehung zwischen Leber- und Gehirnveränderungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **154**:626, 1936; Die Erkrankung der Westphal-Wilsonschen Pseudosclerose als Stoffwechselproblem, Deutsche med. Wchnschr. **66**:1325, 1940.

17. Waggoner, R. W., and Malamud, N.: Wilson's Disease in Light of Cerebral Changes Following Ordinary Acquired Liver Disorders, J. Nerv. & Ment. Dis. **96**:410, 1942.

(Footnotes continued on next page)

had noted lesions in the brain following ligation of the common bile duct and the pancreatic duct in dogs and rats. In the 20 cases finally evaluated by Waggoner and Malamud,[17] cirrhosis of the liver, carcinoma of the pancreas with metastases to the liver, diffuse gummatous hepatitis and pigmentary cirrhosis with hemochromatosis (bronze diabetes) were found to be the commonest hepatic lesions. The clinical picture showed mental symptoms, together with fairly uncharacteristic neurologic signs. Only occasionally was tremor or akinetic phenomena described at the peak of the apparently toxic metabolic disorder. As to the pathologic changes in the central nervous system, the accumulation of Alzheimer glia cells at various sites and spongy necrosis in some instances were said to be the characteristic features.

A similar degenerative necrotizing process in the brain was observed by Woods and Pendleton[19] in 1 of a series of 14 patients who, living in a famine area in China, had sudden appearance of nervous symptoms, some of which were referable to lesions of the brain stem. Autopsy of the liver was not obtained.

In case 20 of Alexander's series reported in his monograph,[20] a picture histologically similar to that characteristic of hepatolenticular degeneration developed in an alcoholic patient with Laennec's (portal) cirrhosis of the liver. Four weeks before his death, in coma, rhythmic tremors developed.

Baker[21] studied the central nervous system in 18 cases of acute, subacute and chronic diseases of the liver, in 8 of which he observed extensive cerebral changes, consisting of damage to nerve cells and widespread areas of predominantly perivascular demyelination. In the history of these cases symptoms of chronic cerebral involvement were not present. The patients became comatose only a few days before death. Baker considered the possibility that an endogenous toxin might have reached the brain and produced the damage in those cases of hepatic disease.

Neurologic changes in cases of the common types of severe hepatic disease without autopsy were reported by Adams and Foley.[22] Three types of clinical phenomena were differentiated: In the first type,

18. Crandall, L. A., Jr., and Weil, A.: Pathology of Central Nervous System in Diseases of the Liver, Arch. Neurol. & Psychiat. **29**:1066 (May) 1933.

19. Woods, A. H., and Pendleton, L.: Fourteen Simultaneous Cases of an Acute Degenerative Striatal Disease, Arch. Neurol. & Psychiat. **13**:549 (May) 1925.

20. Alexander, L.: The Fundamental Types of Histopathologic Changes Encountered in Cases of Athetosis and Paralysis Agitans, A. Research Nerv. & Ment. Dis. Proc. (1940) **21**:334, 1942.

21. Baker, A. B.: The Central Nervous System in Hepatic Disease, J. Neuropath. & Exper. Neurol. **8**:283, 1949.

22. Adams, R. D., and Foley, J. M.: The Neurological Changes in the More Common Types of Severe Liver Disease, Tr. Am. Neurol. A. **74**:217, 1949.

represented by the largest group of cases, hepatic coma terminating in death had developed, the neurologic signs being various degrees of rigidity, grasping and sucking reflexes and an extensor plantar response. The second type was characterized by the same symptoms, but less severe, and recovery followed. The third type, of which there were 3 cases, was characterized by recurrent hepatic stupor. After several episodes a persistent tremor developed. It is significant that the 3 patients never completely recovered normal mental functions during their remissions.

Recently attention has been called to the occurrence of neurologic symptoms in cases of infectious hepatitis. Newman,[23] Cameron,[24] Lescher,[25] Byrne and Taylor [26] and Weinstein and Davison [27] described symptoms referable to peripheral neuritis, meningitis and myelitis. Stokes, Owen and Holmes [28] reported instances of infectious hepatitis with cerebral changes and extrapyramidal signs. In 2 cases in which autopsy was performed, subacute necrosis of the liver and edema of the brain with areas of inflammation, round cell infiltration and extravasation of red blood cells were observed around some vessels in the basal ganglia, as well as in other areas.

At the peak of the metabolic disorder or in the terminal state, all these cases of primary disease of the liver presented a clinical picture distinctly different from the symptoms and course of hepatolenticular degeneration. As is usually observed with severe toxic metabolic disorders, disturbance of consciousness and delirious mental changes were associated with rather nonspecific neurologic signs, and the aforedescribed motor phenomena were never predominant. Considering the chronic progressive course, the corneal ring and the dyskinetic phenomena of hepatolenticular degeneration, it does not seem difficult to differentiate clinically the aforementioned conditions from the rather typical disease entity. Toxic metabolic disorders may affect all parts of the brain diffusely, and it is conceivable that in some instances symptoms referable to the basal ganglia or to the cerebellum or to any other area may appear.

When, in these conditions, acute inflammation with vascular changes dominates the pathologic picture in the central nervous system, the dif-

23. Newman, J. L.: Infective Hepatitis: History of Outbreak in Lavant Valley, Brit. M. J. **1**:61, 1942.

24. Cameron, J. D. S.: Infective Hepatitis, Quart. J. Med. **12**:139, 1943.

25. Lescher, F. G.: Nervous Complications of Infective Hepatitis, Brit. M. J. **1**:554, 1944.

26. Byrne, E. A. J., and Taylor, G. F.: An Outbreak of Jaundice with Signs in Nervous System, Brit. M. J. **1**:477, 1945.

27. Weinstein, L., and Davison, W. T.: Neurologic Manifestations in Preicteric Phase of Infectious Hepatitis, Am. Practitioner **1**:191, 1946.

28. Stokes, J. F.; Owen, J. R., and Holmes, E. G.: Neurological Complications of Infectious Hepatitis, Brit. M. J. **2**:642, 1945.

ferentiation from the process of hepatolenticular degeneration is not difficult. However, in some of the aforementioned observations, the presence of proliferation of Alzheimer glial cells and of foci of necrosis led to the assumption that this process in the toxic metabolic disorders may be of the same nature as the process of hepatolenticular degeneration. Speculation on the pathogenesis and etiology of either disease cannot be based on the presence of the necrotizing cerebral process in both diseases. Wilson [7] explained the difficulties involved and stated:

> . . . this attempt to use tissue-reaction types as a means of dividing "diseases" is one more example of a common fallacy that applies also to nerve cells; poisons and infections are endless but nerve and glia cells are severely restricted in their reactive possibilities. To assume that a particular type of reaction depends on a specific noxa is a mistake.

Only after correlating the specific clinical picture of the chronic progressive disease with specific pathologic lesions in certain areas of the nervous system can one be entitled to assume that a given case belongs to the entity of hepatolenticular degeneration.

It is indeed of particular interest that in hepatolenticular degeneration changes are observed both in the liver and in the central nervous system and, furthermore, that in primary diseases of the liver the nervous system may be affected. The conclusion of Waggoner and Malamud,[17] however, that "Wilson's disease is a primary hepatic disorder which affects the central nervous system secondarily" is not corroborated by this evidence. Our observations revealed only correlations between the intensity of the process in the liver and the severity of the clinical hepatic disturbances, on one side, and the course and progression of the disease, on the other. All questions of etiology and pathogenesis both of the changes in the liver and of those in the brain remain to be answered.

In kernicterus, the cerebral complication of erythroblastosis fetalis, the striking similarity of the localization of the lesions in the basal ganglia to the lesions in hepatolenticular degeneration, has been stressed; in addition, the occurrence of jaundice and disturbances of hepatic function in both conditions was thought to be remarkable. After the discovery of the Rh factor and the realization of its bearing on erythroblastosis fetalis, the entity of kernicterus could be well defined. In addition to the acute phase of kernicterus, the clinical and pathologic sequelae in cases of infants surviving icterus gravis neonatorum with involvement of the central nervous system were recently reported (Zimmerman and Yannet,[29] Leonard,[30] Doctor,[31] Stiller,[32] Lande [33]). It was

29. Zimmerman, H. M., and Yannet, H.: Kernicterus: Jaundice of the Nuclear Masses of the Brain, Am. J. Dis. Child. **45**:740 (April) 1933; Cerebral Sequelae of Icterus Gravis Neonatorum and Their Relation to Kernicterus, ibid. **49**:418 (Feb.) 1935.

uncontestibly proved by determination of the Rh factor in both the parents and the patient that these chronic cases belonged to this group. The cerebral changes consisted of mental deterioration, athetotic movements, cerebellar ataxia and spastic diplegia.

The clinical picture, as well as the pathologic features, in these cases of proved etiology has aroused speculations as to whether some of the processes of the basal ganglia of undetermined origin might not be caused by this clearly recognizable Rh sensitivity, and Zimmerman and Yannet [29] have presented evidence for the possible pathogenesis of status dysmyelinisatus. There are, however, serious doubts as to whether the process of hepatolenticular degeneration can be correlated with kernicterus and Rh sensitivity. The onset of kernicterus in early postnatal life is not in accordance with the onset of hepatolenticular degeneration in the second and third decades of life. The clinical symptoms in the two conditions differ considerably. Furthermore, there is still discussion as to the presence of a primary hepatic disease associated with kernicterus. The mechanism of Rh sensitivity with subsequent hemolysis is regarded as the primary factor, and it is not yet determined whether poor hepatic function, or perhaps constitutional moments, are additional indispensable factors in the production of cerebral lesions in a portion of the cases of erythroblastosis fetalis. Zimmerman and Yannet [29] have never observed cirrhosis of the liver, even in late cases of kernicterus. Further studies of the Rh factors in each parent and in the patient with the so-called degenerative diseases of the basal ganglia might be revealing.

The occurrence of cirrhosis of the liver in domestic animals has been frequently reported (Hutyra, Marek and Manninger [34]). Toxins of certain food plants have been regarded as the causative factor, particularly of Senecio, which produced the lesions when it was fed to animals experimentally. From various parts of the world, cirrhosis of the liver, in swine, sheep, cattle and, particularly, horses has been recognized, and such terms as "Schweinsberg disease" (Germany), "liver staggers" (South Africa), *Dunsckte* (Natal), "walking disease" (the West Coast), "bottom disease" (South Dakota) have been used. The incidence of nervous symptoms in these conditions has been well

30. Leonard, M. F.: Hemolytic Disease of the Newborn, J. Pediat. **27**:249, 1945.

31. Docter, J. M.: Kernicterus: Neurological Sequelae of Erythroblastosis Fetalis, J. Pediat. **27**:327, 1945.

32. Stiller, R.: Kernicterus: A Follow-Up Study of 35 Erythroblastotic Infants, Am. J. Dis. Child. **73**:651 (June) 1947.

33. Lande, L.: Clinical Signs and Development of Survivors of Kernicterus Due to Rh Sensitization, J. Pediat. **32**:692, 1948.

34. Hutyra, F., Marek, J., and Manninger, R.: Special Pathology and Therapeutics of the Diseases of Domestic Animals, ed. 4, London, Baillière, Tindall & Cox, 1938, vol. 2, 388-397.

recognized, and Dobberstein,[35] observing lesions in the nervous system, mentioned the similarity of this process to hepatolenticular disease. Further investigation of diseases of the liver in animals and their relation to the development of lesions in the central nervous system might be of help in the experimental study of the pathogenesis.

SUMMARY

Six cases of hepatolenticular degeneration were studied; in an additional case the characteristic motor phenomena were present but the diagnosis was doubtful.

The significant features of the dyskinetic motor phenomena are described, with motion picture analysis. Spontaneous abnormal involuntary movements may be absent or, if present, may show the characteristics of regular alternating tremor or choreatic, athetotic or dystonic movements. During the maintenance of positions, discoordination ("static intentional ataxia") may be present, or alternating tremor, previously observed "at rest," may be increased in intensity. Both factors may interfere with the performance of fast active movements.

The mechanisms involved in the production of these specific dyskinetic phenomena, in particular the effect of cerebellar disturbances, are discussed.

The clinical findings and laboratory data related to damage to the liver are reported in each case. Neither clinical nor laboratory evidence of impairment of hepatic function was found in 3 cases; laboratory tests gave abnormal results in 4 cases. A positive reaction in the cephalin flocculation test and reduction of serum albumin were the most frequent pathologic findings.

The duration of the disease in this series was correlated with the severity of the damage to the liver. A rather prolonged course, over many years, was observed in some cases in which evidence of hepatic damage was missing or was not pronounced. A rapid progressive course of only one and a half years was found in other cases with obvious symptoms and signs of hepatic impairment.

The pathologic changes in the liver could be studied in 3 cases. In 1 case the chronic process of cirrhosis of the liver with predominant connective tissue proliferation was observed, whereas in 2 cases a rather acute process with necrotic phenomena resembling subacute yellow atrophy was superimposed on the chronic process.

The association of neurologic disorders with "ordinary acquired" hepatic disease in man and the occurrence of peculiar symptoms with cirrhosis of the liver in domestic animals are evaluated, and the differentiation of the symptoms and pathologic picture of these conditions from the typical picture of hepatolenticular degeneration are outlined.

35. Dobberstein, in Joest's Handbuch der speziellen pathologischen Anatomie der Haustiere, Berlin, Richard Schoetz, 1926, vol. 2, p. 594.

ATHETOSIS AND THE BASAL GANGLIA

Review of the Literature and Study of Forty-Two Cases

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GENERAL CONSIDERATIONS

UNDER the term athetosis,[1] Hammond [2] (1871) drew attention to a symptom which he believed had not previously been recognized by medical writers. This symptom was described as "an inability to retain the fingers and toes in any position in which they might be placed, and by their continual motion." Two cases, without autopsy, were reported in which "grotesque," involuntary movements of the fingers and toes occurred unilaterally. Prior to introduction of the term athetosis, almost all abnormal involuntary activity was described as chorea [3] (Oulmont,[4] Herz [5]). Charcot [6] (1853), Heine [7] (1860) and Little [8] (1862) reported abnormal involuntary activity in association with hemiplegia and diplegia, which later authors (Oulmont,[4] Wiszwianski [9]), in retrospect, stated to be similar to that described by Hammond.

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1. ἄθητος, without fixed position.

2. Hammond, W. A.: A Treatise on Diseases of the Nervous System, ed. 1, New York, D. Appleton & Company, 1871, pp. 655-662.

3. χορεία, a choral dance.

4. Oulmont, P.: Étude clinique sur l'athétose, Paris, 1878.

5. Herz, E.: Dystonia: I. Historical Review; Analysis of Dystonic Symptoms and Physiologic Mechanisms Involved, Arch. Neurol. & Psychiat. **51**:305-318 (April) 1944.

6. Charcot, J. M.: Études pour servir à l'histoire de l'affection décrite sous les norms de goutte asthénique primitive, nodosités des jointures, rheumatisme articulaire chronique, Thesis, Paris, no. 44, 1853, p. 537.

7. Heine, J.: Spinale Kinderlähmung, ed. 2, Stuttgart, J. G. Cotta, 1860.

8. Little, W. J.: On the Influence of Abnormal Parturition, Difficult Labours, Premature Birth, and Asphyxia Neonatorum on the Mental and Physical Condition of the Child, Especially in Relation to Deformities, Tr. Obst. Soc., London **3**:293, 1862.

9. Wiszwianski, A.: Beiträge zu der Lehre von der Athetose mit besonderer Berücksichtigung ihres Verhältnisses zu der Chorea und andern ephemiplegischen Bewegungsstörungen, Inaug. Dissert., Würzburg, 1889.

The first description of what is now called double athetosis was given in 1873 by Shaw [10] from several cases without autopsy. Abnormal involuntary activity involving the hands and feet, similar to that described by Hammond, developed soon after birth. In 1896 Anton [11] gave a detailed account of pathologic changes in a case of double athetosis and described abnormal myelinated fibers in the posterior halves of the putamina. Fifteen years later, Oppenheim and Vogt [12] and Freund and Vogt [13] published cases of double athetosis with descriptions of pathologic changes similar to Anton's and called particular attention to the "marbling" of the striatum, which they termed *état marbré*, or "status marmoratus."

Relation of Athetosis to Chorea.—Whether athetosis can be distinguished from chorea has been a subject of much controversy, and many objections were raised to Hammond's use of a specific term for the symptom complex he described. Rosenbach [14] (1876) stated that the differentiation of athetosis from the large group of abnormal involuntary activities was unnecessary. Bernhardt [15] (1876) and Oulmont [4] (1878) considered the athetosis symptom complex as a variety of chorea. Greidenberg [16] (1886) credited Hammond with the naming of athetosis and remarked that hitherto it had not been recognized as an entity and was mistaken for chorea. The same author pointed out that Charcot and his students had described similar activity in infantile cerebral palsy. Charcot [17] (1879) stated the opinion that athetosis was a simple variety of chorea and criticized Hammond's definition. He stated:

> It should be added that the movements of the fingers are performed slowly, and that the fingers have a tendency to assume constraint attitudes. Moreover, the athetosis does not always remain limited to muscles which move the fingers and toes; sometimes, in fact, the entire hand and foot are affected.

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10. Shaw, T. C.: On Athetosis, or Imbecility with Ataxia, St. Barth. Hosp. Rep. **9**:130-140, 1873.

11. Anton, G.: Ueber die Beteiligung der basalen Gehirnganglien bei Bewegungsstörungen insbesondere bei Chorea, Jahrb. f. Psychiat. **14**:141-182, 1896.

12. Oppenheim, H., and Vogt, C.: Nature et localisation de la paralysie pseudobulbaire congénitale et infantile, J. f. Psychol. u. Neurol. (supp.) **18**:293-308, 1911.

13. Freund, C. S., and Vogt, C.: Ein neuer Fall von État marbré des Corpus striatum, J. f. Psychol. u. Neurol. (supp.) **18**:489-500, 1911.

14. Rosenbach, O.: Ist man berechtigt den "Athetose" genannten Symptomencomplex durch einen besonderen Namen auszuzeichnen? Virchows Arch. f. path. Anat. **68**:85-101, 1876.

15. Bernhardt, M.: Ueber den von Hammond Athetose genannten Symptomencomplex, Virchows Arch. f. path. Anat. **67**:1-10, 1876.

16. Greidenberg, B.: Ueber die posthemiplegischen Bewegungsstörungen, Arch. f. Psychiat. **17**:131-216, 1886.

17. Charcot, J. M.: Lectures on the Diseases of the Nervous System, translated by G. Sigerson, Philadelphia, Henry C. Lea, 1879, p. 390.

Bonhoeffer [18] (1897) stated that it was not possible to separate chorea from athetosis because some patients displayed choreoid movements at one time and athetoid movements at another. According to Greidenberg, athetoid movements are so complex and diverse that synthetic descriptions are not possible, although observers have attempted to comprehend and describe the individual movements and their combinations.[19] He stated: "All observers, however, are in agreement on the two cardinal points which characterize and make possible its distinction from other involuntary movements: the type of movement, and its location." Wilson [20] (1925), in his Croonian Lectures, discussed the problem as follows:

> Comparing, now, the symptoms of chorea and athetosis, we find the resemblances more impressive than the differences. In respect of the latter, we have seen that choreic movement is discrete and rapid, while athetoid movement is slow and confluent. But this difference is more apparent than real; athetoid action is slow largely because it is confluent, and, on the other hand, confluent chorea results in slowing of the spontaneous movements. Besides, in some athetosis a degree of discreteness and quickness is observable. In repect of resemblance, in each the type of motor derangement is complex, elaborate, and specialized; changeableness and variability of movement is a prominent trait (i. e., absence of essential repetitiveness); the law of reciprocal innervation is at fault in athetosis and in confluent chorea equally; the movements, caricatures though they are in athetosis more than in chorea, have the appearance none the less in the case of the former of being subjectively purposeful—as for grasping or relinquishing an object, etc.—though they are objectively purposeless.

Herz [21] (1931) studied various dyskinesias, including athetosis, cinematographically. He concluded that athetoid activity was not continuous and was usually preceded by an interval (of highly variable duration) in which increasing tone of antagonistic muscle groups was seen without actual movement. This preliminary phase was succeeded by involuntary activity composed of simultaneous simple and compound movements, producing repeated complex movements. No similarity to synergistic, coordinated activity or purposeful movement could be established, nor was a regular sequence of movement recognized. At the termination of the activity the increased tone of the antagonistic muscle groups was still present but thereafter disappeared.

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18. Bonhoeffer, K.: Ein Beitrag zur Localisation der choreatischen Bewegungen, Monatschr. f. Psychiat. u. Neurol. **1**:6-41, 1897.

19. The value of cinematographic records of abnormal involuntary activity, when supplemented by clinicopathologic studies, has been emphasized by Herz [5] and Whittier (Whittier, J. R.: Ballism and the Subthalamic Nucleus, Arch. Neurol. & Psychiat. **58**:672-692 [Dec.] 1947).

20. Wilson, S. A. K.: Disorders of Motility and Muscle Tone with Special Reference to the Corpus Striatum (Croonian Lectures), Lancet **2**:215-291, 1925.

21. Herz, E.: Die amyostatischen Unruheerscheinungen, J. f. Psychol. u. Neurol. **43**:3-182, 1931.

Although athetosis, chorea and ballism occurring unilaterally are usually termed hemiathetosis, hemichorea and hemiballism, respectively, bilateral chorea and ballism are usually designated simply as chorea and ballism, and bilateral athetosis is usually termed "double athetosis."

Relation of Athetosis to Torsion Dystonia.—Torsion dystonia was first described in 3 siblings by Schwalbe [22] in 1908, as involuntary movements of the upper extremities consisting of rotation or torsion about the long axes with contortions of the hands and torsion movements of the vertebral column. Jakob [23] (1925) stated the belief that torsion spasm and torsion dystonia formed a subtype of athetosis. Alexander [24] (1942) maintained that athetosis and torsion dystonia were the same disease and that differences between them were due to the mechanical differences inherent in the mechanics of axial musculature and of the musculature of the extremities.

Pathologic Changes.—When Hammond first described athetosis, he suggested that the striatum was the site of the pathologic changes. It was not until five years later that Gowers [25] (1876) reported the first autopsy in a case of hemiathetosis. A puckered cicatrix in the contralateral thalamus due to a vascular necrotizing lesion was observed. Since Gowers' report, descriptions of the pathologic picture of athetosis have been numerous and conflicting. Kahler and Pick [26] (1879) stated the belief that athetoid movements were either of cortical origin or due to irritation of the pyramidal tract along its intracerebral course. Bonhoeffer [18] (1897) expressed the belief that lesions in the subthalamic region, especially those in the radiation of the brachium conjunctivum above the red nucleus (*Bindearm-Rothkernstrählung*) were the cause of choreoid and athetoid movements. C. Vogt [27] (1911) stated that the striatum was the site of lesions evoking double athetosis and described the syndrome of the corpus striatum as follows:

> We were thus lead to construct a syndrome of the corpus striatum, consisting of spasms, more or less accompanied with athetoid movements, rhythmic oscillations, associated movements and spasmodic laughing and crying, without (or almost

22. Schwalbe, W.: Eine eigentümliche tonische Krampfform mit hysterischen Symptomen, Inaug. Dissert., Berlin, G. Schade, 1908.

23. Jakob, A.: The Anatomy, Clinical Syndromes and Physiology of the Extrapyramidal System, Arch. Neurol. & Psychiat. **13**:596-620 (May) 1925.

24. Alexander, L.: The Fundamental Types of Histopathological Changes Encountered in Cases of Athetosis and Paralysis Agitans, A. Research Nerv. & Ment. Dis., Proc. **21**:334-383, 1942.

25. Gowers, W. R.: On "Athetosis" and Post-Hemiplegic Disorders of Movement, Med-Chir. Tr. **59**:271-326, 1876.

26. Kahler, O., and Pick, A.: Beiträge zur Pathologie und pathologischen Anatomie des Centralnervensystems, Vrtljschr. f. d. prakt. Heilk. **141**:1-86, 1879.

27. Vogt, C.: Quelques considérations générales à propos du syndrome du corps strié, J. f. Psychol. u. Neurol. **18**:479-488, 1911.

without) paresis, sensory disturbances or impairment of intelligence—in other words, a pure double athetosis.

Later, the Vogts [28] (1920) also described agenesis or imperfect development of the myelin sheaths of the striopallidal fiber systems (*status dysmyelinisatus*) as a cause of athetosis, with or without torsion dystonia. Although Jakob [23] regarded status marmoratus as the only affection of the striatum which produced "pure" athetosis, he stated: "My observations show conclusively that athetoid movements in adults are found only in cases in which there are lesions in the pallidum." In 1929 Schläfli [29] quoted Bing as follows: "Lesions of the putamen tend to produce choreoid hyperkinesia, whereas those of the caudate nucleus tend to produce athetoid hyperkinesia."

It thus appears that there has been general, but not unanimous, acknowledgment that athetoid and dystonic activity follows lesions localized in the basal ganglia. To determine whether athetoid activity as a symptom can be distinguished from other forms of hyperkinesia and to determine what relation, if any, exists between pathologic changes in the basal ganglia and the symptom was our purpose in the present review of the clinical and clinicopathologic literature.

PRESENT STUDY

Athetosis was considered a pattern of discontinuous dyskinesia characterized by slow, involuntary increases and decreases of tone in antagonistic muscle groups (often without apparent movement) and slow, involuntary muscular contractions involving chiefly, but not exclusively, the distal appendicular musculature, such that vermicular or writhing activity resulted. Search was made in the literature for mention of this dyskinetic pattern by name or by description, regardless of the terminology employed, and for the pathologic changes with which it was associated. Descriptions of pathologic alterations in the basal ganglia were also sought, whether accompanied with athetoid activity or not. From these approaches a series of 71 case reports was obtained. Cases (group 2) in which descriptions of the activity and pathologic changes were considered sufficiently complete and accurate were analyzed. The remaining cases (group 1) were considered separately.

GROUP 1.—This group comprises most of the early cases of hemiathetosis and double athetosis, published between 1876 and 1906, which contained both clinical and pathologic data. Although the clinical

28. Vogt, C., and Vogt, O.: Zur Lehre der Erkrankungen des striären Systeme, J. f. Psychol. u. Neurol. (supp.) **25**:627-846, 1920.

29. Schläfli, O.: Ueber lokalisierte choreatische und athetotische Bewegungsautomatismen, Inaug. Dissert., Basel, Ingenbohl, 1929.

TABLE 1.—*Chronology of 24 Reported Cases (Group 1) of Hemiathetosis with Reference to Age at Death, Sex, Location of Neural Lesion and Cause of Death*

Author	Date	Age at Death, Yr.	Sex	Gross Location of Neural Lesion(s)	Cause of Death
Gowers [25]	1876	58	M	Thalamus	Renal disease
Rosenbach [14]	1876	69	F	Lenticular nucleus; posterior columns (cervical cord)	Coronary thrombosis
Ewald [42] (Case 1)	1877	56	M	First temporal convolution	Cerebrovascular accident
(Case 2)	1877	51	M	First frontal convolution; pons (multiple tuberculoma)	Pulmonary tuberculosis
Lauenstein, C.: Deutsches Arch. f. klin. Med. **20**: 153-163, 1877	1877	39	F	Thalamus	Cardiac failure
Landouzy: Progrès méd. **6**: 79-96, 1878	1878	32	F	Lenticular nucleus; cerebral peduncles (atrophy)	Uterine carcinoma
Kuessmer [24]	1878	43	M	No local lesion	Cardiac failure
Gowers [31]	1878	41	F	Thalamus	Cerebrovascular accident
Ringer, S.: Practitioner **23**: 161-176, 1879; footnote 30	1877 1879	34	M	Lenticular nucleus; thalamus; internal capsule	Cardiac failure
Kahler and Pick [26]	1879	62	M	Thalamus; internal capsule; lenticular nucleus	Pneumonia
Murrell, W.: Lancet **1**: 369-370, 1879	1879	33	M	Corpus striatum; internal capsule (hemiatrophy of brain)	Pulmonary tuberculosis
Dreyffous [33]	1879	Infant	..	Corpus striatum (tuberculoma)	Tuberculous meningitis
Demange [43]	1879	46	F	Third frontal convolution (meningioma)	.....
Beach [32]	1880	17	M	Cortex: frontal, parietal, occipital	Not reported
Demange, E.: (Case 2) Rev. de med. **3**: 371-404, 1883	1883	50	M	Cortex: parietal, occipital	Marasmus and decubitus
Roscioli, R.: Gior. di neuropat. **4**: 297-307, 1886	1886	23	M	Thalamus; lenticular nucleus; internal capsule (tuberculoma)	Miliary tuberculosis
Wisrwianski [9]	1889	76	M	Globus pallidus; thalamus; red nucleus	Cerebrovascular accident
Déjerine, cited by Perietzeanu, Thesis, Paris, G. Steinheil, 1900	1892	59	M	Lenticular nucleus; internal capsule; external capsule	Pneumonia
Combe [41]	1892	11	F	Lenticular nucleus (bilateral); second frontal convolution (multiple tuberculoma)	.....
Ferguson, J.: New York State J. Med. **55**: 657, 1892	1892	30	M	Thalamus; internal capsule	.....
Eichhorst, H.: Virchows Arch. f. path. Anat. **137**: 100-120, 1894	1894	56	F	Lenticular nucleus; internal capsule; external capsule	Postoperative thyroidectomy
Sander [44]	1897	38	M	Thalamus (atrophy); pyramidal tract (degeneration)	Cerebrovascular accident
Déjerine, J., and Thomas, A.: Rev. neurol. **8**: 518-521, 1900	1900	61	F	Thalamus; internal capsule	Cerebrovascular accident
Birckenstaedt [40]	1906	32	F	Lenticular nucleus (bilateral); thalamus (left)	Cerebrovascular accident

observations reported in many instances (e. g., Gowers,[25] Ringer,[30] Rosenbach,[14] Kahler and Pick [26]) were adequate, the descriptions of the pathologic changes were not. In most cases no microscopic study was made, and only gross pathologic changes were reported.

Clinical Manifestations.—Twenty-four cases of hemiathetosis and 5 of double athetosis are included in this group (tables 1 and 2).

In 18 cases hemiplegia, often associated with disturbances of sensation and speech, preceded the onset of hemiathetosis or was associated with it. Gowers [31] reported that hemiathetoid activity followed hemiparesis by three and six months respectively in 2 cases. Beach [32] described hemiparesis and convulsive seizures, preceded by trauma, in

TABLE 2.—*Chronology of 5 Reported Cases (Group 1) of Double Athetosis with Data Regarding Age at Death, Sex, Location of Neural Lesion and Cause of Death*

Author	Date	Age, Yr.	Sex	Gross Location of Neural Lesion(s)	Cause of Death
Kirchhoff [35]	1882	60	M	No localized lesion	Cardiac failure
Bernhard [36]	1884	09	M	Corpus striatum (bilateral); thalamus (bilateral)	Multiple fractures
Déjerine and Sollier [37]	1888	34	M	Lenticular nucleus (right); parietal cortex (left, atrophy)	Tuberculous meningitis
Putnam [38]	1892	13	F	Lenticular nucleus (left); temporal lobe (right, abscess)	Not reported
Eisenlohr [39]	1893	68	F	Spinal cord (bilateral) (cervical region)	Pneumonia

TABLE 3.—*Age Distribution of Patients (Group 1) at Onset of Symptoms (Hemiathetosis Associated with Hemiparesis)*

	Age Group, Decade							
	1-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79
No. of cases.....	3	2	1	4	1	4	2	1

his case of hemiathetoid activity. The average age of the 18 patients at the onset of symptoms was 37, and the age distribution was random (table 3). Twelve patients were males, and 6 were females.

Spontaneous onset of hemiathetoid activity without paresis or sensory disturbances was described in 6 cases. In 1 of these (Dreyffous [33])

30. Ringer, S.: Notes on a Case of Athetosis, Preceded by Hemiplegia and Hemianæsthesia, and Accompanied by Unilateral Sweating, Practitioner **19**:90-108, 1877.

31. Gowers, W. R.: On Some Symptoms of Organic Brain Disease, Brain **1**:48-59, 1878; footnote 25.

32. Beach, F.: An Account of the Microscopical Appearances in a Case of Athetosis, Brit. M. J. **1**:967, 1880.

33. Dreyffous: Hémiathétose du membre supérieur gauche, Thesis, Paris, 1879; cited by Perietzeanu, J.: Contribution à l'étude anatomopathologique et clinique de l'hémiathétose, Thesis, Paris, G. Steinheil, 1900.

signs of meningitis were present. Kuessner's [34] patient was said to have sustained three cerebral vascular attacks (*Anfallen*) without the development of paresis; after the third he had a transitory aphasia.

Double athetosis, most pronounced in the distal portions of the upper extremities, which developed in association with mild paresis in 2 cases in the sixth decade of life, was described by Kirchhoff [35] and Bernhard.[36] In the case reported by Kirchhoff the athetoid activity, more prominent on the left, appeared spontaneously during the night. Déjerine and Sollier,[37] Putnam [38] and Eisenlohr [39] reported cases of double athetosis with onset at the ages of 3 years, 18 months and 18 weeks, respectively.

Pathologic Changes.—Destruction of neural tissue in 17 of the 24 cases of hemiathetosis was due to necrotizing cerebrovascular lesions. Destruction was localized grossly in the lenticular nucleus, but coexisting or antecedent pathologic changes elsewhere occurred in 10 of these 17 cases, the adjacent structures damaged including the internal capsule, the lateral part of the thalamus and the red nucleus. In 4 cases destruction localized grossly in the thalamus, particularly the posterolateral portion, was described, but coexisting damage to adjacent structures (e. g., the internal capsule) was common. Necrotizing cerebrovascular lesions in various portions of the cerebral cortex were described in 3 cases. Destruction of neural tissue was contralateral to the side of the symptoms in all cases except that of Birckenstaedt,[40] in which lesions occurred in the lenticular nucleus bilaterally.

Gross examination of the brains in 5 cases revealed tumors. In 4 cases these were identified as tuberculomas, and in the fifth case the description suggested a meningioma. Tuberculomas in 3 cases were described in the region of the lenticular nucleus, but coexisting pathologic changes were noted elsewhere, particularly in adjacent structures (e. g., the internal capsule and the lateral portion of the thalamus) and

34. Kuessner, B.: "Athetose" Bewegungen bei einem Paralytiker ohne Herderkrankung im Gehirn, Arch. f. Psychiat. **8**:443-450, 1878.

35. Kirchhoff: Acute linksseitige Hemiathetose ohne Herderkrankung, Arch. f. Psychiat. **13**:582-589, 1882.

36. Bernhard, H.: Ueber Athetose, Inaug. Dissert., Würzburg, 1884; cited by Audry, J.: L'athétose double et les chorées chroniques de l'enfance, Paris, J.-B. Baillière & fils, 1892.

37. Déjerine, J., and Sollier, P.: Premier cas d'autopsie d'athétose double datant de la première enfance, Bull. Soc. Anat. de Paris, 1888; summary cited by Audry, J.: L'athétose double et les chorées chroniques de l'enfance, Paris, J.-B. Baillière & fils, 1892.

38. Putnam, J. W.: A Case of Complete Athetosis with Postmortem, J. Nerv. & Ment. Dis. **19**:124-126, 1892.

39. Eisenlohr, C.: Zur pathologischen Anatomie der Athetose, Jahrb. d. Hamb. Staatskrankenanst. **4** (pt. 2):22-40, 1893-1894.

40. Birckenstaedt, A.: Ueber Athetose, Inaug. Dissert., Leipzig, 1906.

in the cortex. Combe [41] reported tuberculomas in the lenticular nucleus bilaterally and in the second right frontal convolution, but athetoid movements were observed only on the left side. Ewald,[42] in his case 2, described two tuberculomas in different stages of development contralateral to the side of the athetoid activity; one was located in the first frontal convolution, and the other (of more recent development) was in the pons and extended rostrally to the level of the substantia nigra. Demange [43] reported multiple small tumors, contralateral to the side of athetoid activity, in the third frontal convolution and along the superior sagittal sinus. No identification of these tumors was made, but their description suggested meningioma. Unilateral atrophy of the thalamus (contralateral to the side of activity) with degeneration of the pyramids was reported by Sander.[44] Kuessner [34] failed to identify any gross lesion in a case of hemiathetosis.

Necrotizing vascular lesions were reported by Déjerine and Sollier,[37] Putnam [38] and Eisenlohr [39] in cases of double athetosis (for location of the gross lesions,[38] see table 2). In Bernhard's case autopsy revealed bilateral symmetric atrophy of the striatum and thalamus, except for the anterior nucleus. Kirchhoff [35] was unable to find any localized lesion at autopsy in his case, but he noted that the brain was edematous and icteric (cirrhosis of the liver was observed).

The commonest causes of death (tables 1 and 2) were cerebrovascular disease, tuberculosis, cardiac failure and pneumonia. In 3 of the 5 cases of death from tuberculosis, cerebral tuberculomas were observed at autopsy.

GROUP 2.—On the basis of clinical manifestations, the cases were classified under hemiathetosis, double athetosis and double athetosis with torsion dystonia.

Hemiathetosis.—Clinical Manifestations: Eight cases of hemiathetosis (table 4) which satisfied the criteria of this study were found in the literature.

In 2 cases hemiathetosis followed hemiparesis developing in early childhood. In Berger's [45] case the patient at the age of 3 years suffered

41. Combe: Contribution à l'étude de l'hémiathétose primaire, Rev. méd. de la Suisse Rom. **7**:686-696, 1892; cited by Perietzeanu, J.: Contribution à l'étude anatomo-pathologique et clinique de l'hémiathétose, Thesis, Paris, G. Steinheil, 1900.

42. Ewald, C. A.: Zwei Fälle chronischer Zwangsbewegungen, Deutsche Arch. f. klin. Med. **19**:591-615, 1877.

43. Demange, E.: Hémiathétose limitée au membre superieur gauche, Rev. méd. de l'est., 1879; cited by Perietzeanu, J.: Contribution à l'étude anatomo-pathologique et clinique de l'hémiathétose, Thesis, Paris, G. Steinheil, 1900.

44. Sander, M.: Ein Fall von Athetose mit Sectionsbefund, Neurol. Centralbl. **16**:301-308, 1897.

45. Berger, A.: Zur Kenntnis der Athetose, Jahrb. f. Psychiat. **23**:214-233, 1903.

a cerebrovascular accident in which sudden loss of consciousness was immediately followed by hemiparesis. In both cases it was impossible to determine the interval between onset of hemiparesis and onset of hemiathetosis. In 1 case (Herz [46]) the patient had had slight weakness and involuntary activity on the right side of the body as long as she could remember. At the age of 30 paresis of the left upper extremity and the left half of the face developed, and jacksonian seizures began. The athetoid activity on the right side persisted unchanged until her death, one year later. In 4 cases (Muratow,[47] Steck,[48] Richter [49] [case 3], Kamin [50]) with hypertensive vascular disease and arteriosclerosis the hemiparesis, followed by hemiathetosis, had its onset after the age of 50. In Muratow's case tremor (*Zitterbewegungen*) appeared in the affected arm about three weeks after hemiparesis and was gradually replaced by athetoid activity. In Richter's case athetoid activity appeared on the affected side a little more than two weeks after hemi-

TABLE 4.—*Chronology of 8 Reported Cases (Group 2) of Hemiathetosis with Data Regarding Sex, Age at Onset, Age at Death and Cause of Death*

Author	Date	Sex	Age at Onset, Yr.	Age at Death, Yr.	Cause of Death
Haenel [52]	1902	M	Early childhood	21	Pulmonary tuberculosis
Berger [45]	1903	M	3	62	Gastric carcinoma
Muratow [47]	1908	M	50	54	Cerebrovascular accident
Herz [46]	1911	F	Birth (?)	31	Pulmonary tuberculosis
Steck [48]	1921	F	50	67	Endocarditis
Richter [49] (Case 3)	1923	M	53	56	Cardiac failure
Kamin [50]	1931	F	77	78	Cardiac failure
Thomas [51]	1932	M	34	65	Unreported

paresis. In 2 cases (Steck, Kamin) abnormal movements did not develop after the first apoplectic seizure, but cerebrovascular disturbances three and twenty years later, respectively, were followed by athetoid activity on the affected side. In a case described by Thomas [51] hemiathetosis developed after hemiparesis attributed to trauma.

46. Herz, A.: Zur Frage der Athetose bei Thalamuserkrankungen, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **18**:346-360, 1911.

47. Muratow, W. A.: Beitrag zur Pathologie der Zwangsbewegung bei zerebralen Herderkrankungen, Monatschr. f. Psychiat. u. Neurol. **23**:510-528, 1908.

48. Steck, H.: Zur pathologischen Anatomie der echten posthemiplegischen Athetose, Schweiz. Arch. f. Neurol. u. Psychiat. **8**:75-85, 1921.

49. Richter, H.: Beiträge zur Klinik und pathologischen Anatomie der extrapyramidalen Bewegungsstörungen, Arch. f. Psychiat. **67**:226-294, 1923.

50. Kamin, M.: Zur Lokalisationsfrage der posthemiplegischen Athetose, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **33**:177-188, 1931.

51. Thomas, J. M.: Posthemiplegic Athetosis: Report of a Case; Rôle of Corticospinal Pathways in Production of Choreiform and Athetoid Movements, Arch. Neurol. & Psychiat. **28**:1091-1103 (Nov.) 1932.

Athetoid movements in all cases were most marked in the distal portions of the upper extremity but were present also in the lower extremity. The proximal appendicular muscles and muscles of the trunk were not involved. In only 2 cases (Berger,[45] Herz [46]) was athetoid activity seen in the face. In Berger's case athetoid activity was observed initially in the face, hand and foot, and in time it gradually disappeared from the foot. Although athetoid movements persisted for fifty-seven years in one half of the face and in one upper extremity, the patient was able to work in the vineyards. At 60 years of age the athetoid activity became so intense that he could no longer work. In Thomas' case slow vermicular movements were seen in both arms and in one leg just prior to the patient's death.

Descriptions of the involuntary activity follow. "The movements are slow and somewhat purposeful, as though the patient wanted to grasp something or to play the piano [Berger [45]]." "The entire extremity, especially the hand, is in almost continual athetoid movement (alternate spreading of the fingers, flexion and extension of the distal phalanges, adduction and opposition of the thumb, etc.) [Haenel [52]]."

Athetoid movements in the fingers, hand and arm were so severe in Richter's case that the patient was unable to hold objects with the affected hand or to feed himself. The athetoid movements were aggravated by emotional disturbances and during observation by another, speaking, walking and the performance of voluntary activity, but disappeared during sleep. Berger commented, however: "They [the movements] were continuous, becoming somewhat weaker but not ceasing during sleep."

Although hemiparesis was present in all cases, spasticity (increased resistance to passive movement) was noted as present in 5 cases (Haenel, Muratow, Richter, Herz, Steck), and was present by inference in 2 cases (Kamin, Thomas). Muscular atrophy was present in 3 cases (Haenel, Herz, Steck). In 1 case (Herz) the muscles of the shoulder girdle were atrophic, and in 2 cases hemiatrophy of the paretic side was reported (Steck, Haenel). Contracture of the fingers in flexion was reported in 1 case, and equinovarus was seen in 2 cases. Sensory disturbances in the paretic side were reported in 4 cases. In 1 case pain was complained of in the upper extremity alone and on the affected side of the body in 3 cases. In 3 cases (Muratow, Herz, Steck) examination disclosed diminished deep sensibility, astereognosis and impaired proprioceptive localization in the affected limbs. In 1 case (Richter) there was complaint of coldness and painful paresthesia (*Nadelstiche*) on the paretic side, and sensory examination revealed hyperesthesia and

52. Haenel, H.: Zur pathologischen Anatomie der Hemiathetose, Deutsche Ztschr. f. Nervenh. **21**:28-47, 1902.

hyperalgesia. Temporary disturbances of speech (aphasia) in 2 cases (Steck, Kamin) appeared after left hemiparesis but subsequently disappeared. Dysarthria, noted in 1 case (Muratow), gave the impression that the patient was speaking with a full mouth. Convulsive seizures were reported in 2 of the 8 cases (Thomas, Herz). Although in 1 case the patient was of low intelligence before onset of the symptoms, no mental impairment or psychic disturbance was reported.

Pathologic Changes: In 8 cases hemiparesis was attributable to vascular disturbances which produced necrotizing lesions in the internal capsule and adjacent neural structures contralateral to the symptoms. The other neural structures primarily involved, in addition to the internal

TABLE 5.—*Location of Neural Lesions in 8 Reported Cases (Group 2) of Hemiathetosis*

Author	Date	Primary (Area(s) Affected *	Sites of Other Lesions
Haenel [52]	1902	Subthalamic region; internal capsule	.....
Berger [45]	1903	Putamen internal capsule	.....
Muratow [47]	1908	Thalamus (lateral nucleus); internal capsule; brachium conjunctivum; substantia reticularis	Corpus callosum (gumma of splenium)
Herz [46]	1911	Thalamus (lateral nucleus); brachium conjunctivum; dentate nucleus (atrophy)	Contralateral precentral gyrus (tuberculoma)
Steck [48]	1921	Caudate nucleus (corpus) putamen; internal capsule	Subthalamic nucleus; thalamus (lateral nucleus)
Richter [49] (Case 3) (p. 238)	1923	Caudate nucleus; putamen; thalamus (lateral nucleus); internal capsule	.....
Kamin [50]	1931	Caudate nucleus (caput); putamen; internal capsule	Cortex: parietal, occipital, temporal, insular (old softening)
Thomas [51]	1932	Caudate nucleus; putamen; globus pallidus; internal capsule	Cortex: precentral gyrus, frontal cortex, subthalamic nucleus

* Pathologic changes were contralateral to symptoms unless noted.

capsule, were, in the order of frequency (table 5), the putamen (5 cases), the caudate nucleus (4 cases), the lateral nucleus of the thalamus (2 cases), the globus pallidus (1 case) and the cortex (1 case).

The most frequent combination of structures damaged was the internal capsule, the caudate nucleus and the putamen (4 cases). In Herz's [46] case (athetoid activity present in the right arm and hand as long as the patient could remember) a large area of old softening was noted in the anterior and middle thirds of the lateral nucleus of the thalamus on the left. Degeneration (Weigert stain) could be followed from the lateral nucleus of the thalamus to the red nucleus, the brachium conjunctivum and the dentate nucleus of the opposite side. Paresis of the left upper extremity and the left side of the face and jacksonian

seizures, also present, were attributed to a tuberculoma observed in the right anterior central gyrus. In Muratow's case the lesion was also located in the lateral nucleus of the thalamus. It involved the posterior limb of the internal capsule, the reticular substance and the upper reaches of the left brachium conjunctivum. Degeneration (Weigert stain) of the brachium conjunctivum could not be followed beyond the decussation.

A lesion in the subthalamic region and the internal capsule was found contralateral to the side of athetoid activity in Haenel's case. Degenerative changes were also noted in the subthalamic nucleus in the cases of Steck and Thomas. In 4 cases hyperesthesia, hyperalgesia and disturbances in proprioceptive sensation were correlated with lesions in the lateral nucleus of the thalamus (Richter, Muratow, Herz, Steck). In Haenel's case athetoid activity was present despite complete secondary degeneration (Weigert stain) of the pyramidal tract on the affected side. Athetoid movements continued in Thomas' case in parts of a limb deprived of corticospinal tract connections (medial two fifths of the cerebral peduncle contralateral to the abnormal activity was completely degenerated [modified Kulschitzky stain]).

Double Athetosis.—Clinical Manifestations: Twenty-six cases (table 6) of double athetosis which satisfied the criteria of this study were found in the literature. In 13 cases double athetosis was present from birth (Oppenheim and Vogt [12] [cases 1 and 2]; Filiminoff [53]; Bielschowsky [54]; Pfeiffer [55]; Onari [56] [cases 1 and 2]; Scharapow and Tschernomordik [57] [case 1]; Meyer [58]; Kreyenberg [59]; Holzer [60]; Papez, Hertzman and Rundles [61]; Neustaedter [62] [case 1]). The following

53. Filiminoff, I. N.: Zur klinischen und pathologo-anatomischen Charakteristik der doppelseitigen Athetose des Kindesalters, Ztschr. f. d. ges. Neurol. u. Psychiat. **78**:197-218, 1922.

54. Bielschowsky, M.: Ueber den Status marmoratus des Striatum und atypische Markfasergeflechte der Hirnrinde, J. f. Psychol. u. Neurol. **31**:125-151, 1924.

55. Pfeiffer, F.: Chorea-Athetose bei der Little-Lähmung, Arch. f. Psychiat. u. Nervenh. **72**:728-754, 1925.

56. Onari, K.: Ueber zwei klinische und anatomische kompliziert liegende Fälle von Status marmoratus des Striatum, Ztschr. f. d. ges. Neurol. u. Psychiat. **98**:457-486, 1925.

57. Scharapow, B. I., and Tschernomordik, P. M.: Zur Pathologie der Stammganglien, J. f. Psychol. u. Neurol. **35**:279-282, 1928.

58. Meyer, A.: Zur Auffassung des Status marmoratus, Ztschr. f. d. ges. Neurol. u. Psychiat. **100**:529-544, 1926.

59. Kreyenberg, G.: Status dysmyelinisatus des Pallidum bei congenitaler bilateraler Athetose, Ztschr. f. d. ges. Neurol. u. Psychiat. **132**:806-814, 1931.

60. Holzer, R.: Ueber das Vorkommen des Status marmoratus in Thalamus opticus, Ztschr. f. d. ges. Neurol. u. Psychiat. **151**:696-699, 1934.

61. Papez, J. W.; Hertzman, J., and Rundles, R. W.: Athetosis and Pallidal Deficiency, Arch. Neurol. & Psychiat. **40**:789-799 (Oct.) 1938.

62. Neustaedter, M.: Choreo-Athetosis and Athetosis (Clinicopathologic Report), Dis. Nerv. System **4**:6-10, 1943.

complications were recorded in connection with the births in these cases: artificially induced labor (Meyer); asphyxia (Onari, case 2); forceps delivery (Pfeiffer; Scharapow and Tschernomordik, case 1); precipitous

TABLE 6.—*Chronology of 26 Reported Cases (Group 2) of Double Athetosis with Reference to Sex, Age at Onset, Age at Death and Cause of Death*

Author	Date	Sex	Age at Onset	Age at Death, Yr.	Cause of Death
Anton [11]	1896	M	9 mo.	9	Not reported
Oppenheim and Vogt [12]					
Case 1	1911	F	Birth	23	Pulmonary tuberculosis
Case 2	1911	F	Birth	24	Peritonitis
Freund and Vogt [13]	1911	F	5 yr.	77	Cardiac failure
Fischer [42]	1911	M	15 yr.	21	Pulmonary tuberculosis
Vogt and Vogt [28]					
Case 1	1920	F	3 yr.	59	Suicide
Case 4	1920	M	2 yr.	38	Pulmonary edema
Case 20	1920	M	6 mo.	9	Not reported
Filiminoff [53]	1922	M	Birth	21	Exhaustion and marasmus
Bielschowsky [54]	1924	M	Birth	8	Bronchopneumonia
Scholz [44]	1924	F	11 mo.	7	Pneumonia
Pfeiffer [55]	1925	M	Birth	15	Not reported
Onari [56]					
Case 1	1925	F	Birth	41	Marasmus and bronchopneumonia
Case 2	1925	M	Birth	18	Marasmus and decubitus
Meyer [52]	1926	F	Birth	7	Marasmus
Scharapow and Tschernomordik [57]					
Case 1	1928	M	Birth	6	Scarlet fever
Case 2	1928	F	3 mo.	6	Convulsions (?)
van Bogaert [45]					
Case 4	1929	F	3 yr.	17	Bronchopneumonia
Crothers and Cobb [46]	1930	M	13 mo.	6	Pneumonia
Kreyenberg [59]	1931	M	Birth	28	Peritonitis
Gozzano [47]	1934	M	25 yr.	57	Bronchopneumonia
Holzer [60]	1934	(?)	Birth	4	Scarlet fever
Papez, Hertzman and Rundles [61]	1938	F	Birth	35	Bronchopneumonia
Neustaedter [62]					
Case 1	1943	F	Birth	38	Pneumonia
Case 2	1943	M	?	55	Pneumonia
Christensen and Stubbe Teglbjærg [48]	1946	M	2 yr.	74	Old age (?)

labor (Papez, Hertzman and Rundles); premature birth (Filiminoff); protracted and difficult labor (Holzer). Convulsions immediately after birth were seen in 2 cases (Onari, case 2; Scharapow and Tschernomordik, case 1), and fever after birth occurred in 1 case (Bielschowsky [54]).

A period of apparently normal growth and development preceded the onset of double athetosis in 13 cases (Anton,[11] Freund and Vogt,[13] Fischer,[63] Vogt and Vogt [28] [cases 1, 4, and 20], Scholz,[64] Scharapow and Tschernomordik [57] [case 2], Neustaedter [62] [case 2], van Bogaert [65] [case 4], Crothers and Cobb,[66] Gozzano,[67] Christensen and Stubbe Teglbjærg [68]). The intervals of apparently normal development (table 6) prior to the onset of double athetosis ranged from three months to twenty-five years. Asphyxia at birth was reported in 3 of the latter 13 cases (Vogt and Vogt [28] [case 1], Scharapow and Eschernomordik [case 2], Crothers and Cobb), and protracted and difficult labor was reported by Vogt and Vogt (case 20). Convulsive seizures occurred soon after birth in a case described by Christensen and Stubbe Teglbjærg.

The initial symptoms found in these cases were inability to hold the head erect, inability to sit up, general restlessness, involuntary clenching of the fists, involuntary spreading of the fingers, awkwardness in performance of skilled movements and disturbances of gait. In 9 of the 26 cases general development was impaired or arrested. Kreyenberg commented on his patient as follows: "One year after birth he appeared the same as at 2 months." In a case reported by Scholz, paresis and double athetosis developed at 11 months of age, after high fever of unknown cause.

Athetoid activity was bilateral and most pronounced in the distal portions of the upper extremity. The tongue, face and neck were affected as frequently as the lower extremities, but usually more severely. An exception was noted in the case of Freund and Vogt,[13] in which athetoid activity was present in the right upper extremity and the distal portions of both lower extremities. The involuntary movements were complex, slow and writhing and, although repetitive, followed no regular rhythm. Bizarre contortions and deformity of the digits and hands resulted from the irregular twisting movements. Attention, emotion, external restraint and attempts to speak or to execute volitional move-

63. Fischer, O.: Zur Frage der anatomischen Grundlage der Athétose double und der post-hemiplegischen Bewegungsstörung überhaupt, Ztschr. f. d. ges. Neurol. u. Psychiat. **7**:463-486, 1911.

64. Scholz, W.: Zur Kenntnis des Status marmoratus, Ztschr. f. d. ges. Neurol. u. Psychiat. **88**:355-382, 1924.

65. van Bogaert, L.: Sur une varieté non décrite d'affection familiale: L'épilepsie myoclonique avec choréo-athétose, Rev. neurol. **52**:385-414, 1929.

66. Crothers, B., and Cobb, S.: Progressive Athetosis with Lesions in Basal Ganglion: Case, New England J. Med. **203**:213-218, 1930.

67. Gozzano, M.: Studio anatomo-clinico di un caso di atetosi doppia, Riv. di pat. nerv. **43**:41-48, 1934.

68. Christensen, E., and Stubbe Teglbjærg, H. P.: Double Athetosis with Status Marmoratus, Acta psychiat. et neurol. **21**:177-194, 1946.

ments exacerbated the athetoid activity, which tended to be continuous. Sedatives usually decreased the abnormal activity, and sleep brought complete cessation.

The entire upper extremity, especially the hand, was in almost continuous slow movement, e. g., wide spreading of the fingers, flexion and extension of the fingers and adduction and opposition of the thumb. The wrist was strongly flexed or hyperextended, and the digits were extended or hyperextended at the metacarpophalangeal joints. The interphalangeal joints were flexed, or extended, or some were flexed and some extended. The arm was usually held slightly adducted, with the elbow flexed. The muscles of the shoulder, pelvis and trunk were occasionally affected, but only to a slight degree. In the face, slow grimacing and muscular spasm produced distortion of the features, and lingual athetosis gave rise to hesitant dysarthria. The muscles concerned with swallowing were often similarly affected, causing food to be retained in the mouth and frequently regurgitated. Athetoid activity in the lower extremities was most pronounced in the toes and ankles. Pes planus and equinovarus were often observed.

No paresis was found in the cases of Anton, Fischer, Vogt and Vogt (case 4), Meyer, and Christensen and Stubbe Teglbjærg. Paresis of varying degrees accompanied double athetosis in the cases of Oppenheim and Vogt (cases 1 and 2), Freund and Vogt (unilateral), Filiminoff, Scharapow and Tschernomordik (case 2), Crothers and Cobb, Pfeiffer, Scholz, Onari (cases 1 and 2) and Kreyenberg. Vogt and Vcgt, in case 1, reported no paresis until the age of 58, when the patient suffered right hemiplegia. Paresis was usually more pronounced in the lower extremities.

Spasticity (increased resistance to passive movement) was noted as present in the cases of Freund and Vogt; Vogt and Vogt (case 20); Bielschowsky; Scharapow and Tschernomordik (case 2); Crothers and Cobb; Papez, Hertzman and Rundles; Christensen and Stubbe Teglbjærg; Gozzano; Pfeiffer; Scholz; Onari (cases 1 and 2), and Kreyenberg and was present by inference in the second case of Oppenheim and Vogt.

Inability to walk was noted as present in 9 cases and was present by inference in 4 others. In 4 other cases the child did not learn to walk until after the age of 5 years. Those who were able to walk had a slow, distorted gait. The trunk was thrust forward or backward; the arms were adducted, flexed and pronated or extended and pronated; the wrists were flexed and turned inward, and the legs were internally rotated and adducted. The step was small, slow and insecure. Athetoid activity in the digits and hands was aggravated and occasionally brusque.

Although muscular development was in most cases generally poor, atrophy of muscular groups was present (by inference) in only 2 instances. Sensory disturbances were never noted.

Either dysarthria or retarded speech development was reported in 21 of these 26 cases. Five patients never learned to speak at all. In a case described by Kreyenberg [59] the patient spoke his first word at 11 years of age and thereafter spoke only in monosyllables. Speech was usually hesitant, inarticulate, jerky, labored and in some instances monosyllabic and incomprehensible. Christensen and Stubbe Teglbjærg [68] described their patient as follows:

"The patient opened his mouth widely, hesitated, made a few inarticulate sounds and then spoke several words that were unintelligible except to those acquainted with him."

Fifteen of the 26 patients were mentally defective. Six were considered of normal intelligence, and pertinent data were lacking on the rest. Several patients showed disorientation, emotional instability and inappropriate affect. The condition of 1 patient (Onari,[56] case 1) was diagnosed as schizophrenia at the age of 35.

Pathologic Changes: Bilateral status marmoratus (*état marbré*) of the striatum (caudate nucleus and putamen) was described in 16 of the 26 cases (tables 7 and 8). The marbling fibers were confined to the striatum exclusively, without coexisting or antecedent pathologic change elsewhere, in 7 cases (Anton, Oppenheim and Vogt [case 2], Freund and Vogt, Scholz, Scharapow and Tschernomordik [case 1], van Bogaert [case 4], Christensen and Stubbe Teglbjærg). All authors described reductions in the volume of portions of the striatum and fine abnormal myelin fibers in bundles and netlike configurations, such that in Weigert preparations (or similar stains for myelin) a characteristic marble-like appearance resulted. Reductions in the number of small and large ganglion cells and increases in small glial nuclei and fibers were reported in 4 of these cases.

Status marmoratus of the striatum and thalamus and of the striatum, thalamus and globus pallidus were each described once (Gozzano, Meyer). Status marmoratus of the striatum and thalamus coexisted with status dysmyelinisatus of the globus pallidus in a case described by Onari [56] (case 1). Gozzano's case was complicated by four tumors, which were inadequately described with regard to location and histologic features. The ganglion cells of the thalamus and striatum were described in "various degrees of chronic alteration." No increase in glial nuclei or fibers was described. Meyer [58] reported an "endarteritis of blood vessels in the putamen" with increased glial nuclei and fibers in their

TABLE 7.—*Location of Neural Lesions in 26 Reported Cases (Group 2) of Double Athetosis*

Author	Date	Location of Principel Lesion(s) (Bilateral)*	Sites of Other Lesions (Bilateral)*
Anton [11]	1906	Putamen †	
Oppenheim and Vogt [12]			
Case 1	1911	Precentral gyrus	Microgyria cortex: Frontal; parietal; temporal
Case 2	1911	Striatum †	
Freund and Vogt [13]	1911	Striatum †	
Fischer [45]	1911	Globus palliudus	
Vogt and Vogt [28]			
Case 1	1920	Putamen †	Cortex (fibromyelin plaques)
Case 4	1920	Striatum †	Subthalamic nucleus (reduced in volume)
Case 20	1920	Globus pallidus (status dysmyelinisatus)	Subthalamic nucleus; thalamus (lateral nucleus)
Filiminoff [52]	1922	Precentral gyrus; striatum	
Bielschowsky [54]	1924	Caudate nucleus (right)†; putamen †	Cortex (fibromyelin plaques)
Scholz [64]	1924	Striatum †	
Pfeiffer [55]	1925	Striatum †; thalamus (atrophy)	
Onari [56]			
Case 1	1925	Striatum †; thalamus †; globus pallidus (status dysmyelinisatus)	Red nucleus; subthalamic nucleus (reduced in volume)
Case 2	1925	Striatum †	Corpus callosum (atrophy)
Meyer [58]	1926	Striatum †; globus pallidus †; thalamus (lateral nucleus)†	
Scharapow and Tschernomordik [57]			
Case 1	1928	Putamen †	
Case 2	1928	Globus pallidus	
van Bogaert [65] (Case 4)	1929	Putamen †	
Crothers and Cobb [66]	1930	Striatum; globus pallidus; thalamus	Cortex (anomaly of the gyri)
Kreyenberg [59]	1931	Globus pallidus (status dysmyelinisatus)	
Gozzano [67]	1934	Striatum †; thalamus †	Tumors(?), cortex (fibromyelin plaques)
Holzer [60]	1934	Putamen †; subthalamic nucleus (20% destroyed)	Thalamus: centromedian nucleus ("sclerotic")
Papez, Hertzman and Rundles [61]	1938	Globus pallidus	
Neustaedter [62]			
Case 1	1943	Striatum	Dentate nucleus; red nucleus
Case 2	1943	Striatum	Dentate nucleus; red nucleus
Christensen and Stubbe Teglbjærg [68]	1946	Striatum †	

* Lesions not bilateral are so noted.
† Status marmoratus.

TABLE 8.—*Approximate Localization of Status Marmoratus Within the Striatum in 16 Reported Cases (Group 2) of Double Athetosis*

Caudate Nucleus			Putamen *			
Head	Body	Tail	Anterior Portion	Middle Portion	Posterior Portion	Total
11	0	0	9	2	4	1

* Portions of the putamen were involved in all cases.

vicinity. The lateral nucleus of the thalamus was severely degenerated and contained a small cyst. Onari described bilateral atrophy of the caudate nucleus and lateral nucleus of the thalamus in his case of status marmoratus (case 1). The number of large and small ganglion cells of the striatum were greatly reduced, and many of those remaining were in phases of neuronophagia. Within the globus pallidus a distinct reduction of myelin fibers was described, and the volume of the various divisions of the ansa lenticularis was abnormally small. The ganglion cells of the pallidum were pale but otherwise normal. Increased numbers of small glial nuclei were seen in the striatum, in the lateral nucleus of the thalamus and in the globus pallidus, particularly near blood vessels. The descriptions of the fine, abnormal myelin fibers in the striatum were the same as in the cases discussed in the preceding paragraph.

Vogt and Vogt (case 1), Bielschowsky and Gozzano reported fibromyelin plaques of the cerebral cortex, in addition to status marmoratus of the striatum. Bielschowsky described these fibromyelin plaques as located in the lower cortical laminas and consisting of small accumulations of glial cells and myelin fibers which radiated toward the surface. The cytoarchitecture was atypical in their vicinity, and ganglion cells were missing where the myelin fibers were well developed.

In 4 cases status marmoratus of the striatum coexisted with noteworthy pathologic changes elsewhere. Pronounced bilateral atrophy of the thalamus without "marbling fibers" was associated with status marmoratus of the striatum in a case reported by Pfeiffer. In Onari's case 2 atrophy of the corpus callosum coexisted with status marmoratus of the striatum. Holzer described bilateral "degeneration" of approximately 20 per cent of the subthalamic nucleus (corpus Luysi) and "sclerosis" of the nucleus centralis thalami (centromedian nucleus of the thalamus), in addition to status marmoratus of the striatum. The Vogts,[28] in their fourth case, remarked that the subthalamic nuclei were "undoubtedly smaller than normal."

Bilateral pathologic changes in the striatum, other than status marmoratus, with coexisting or antecedent pathologic changes elsewhere, were described in 3 of these 26 cases. Crothers and Cobb reported bilateral gross atrophy of the striatum, thalamus and globus pallidus in association with an anomalous pattern of cortical convolutions in the frontal and temporal lobes. Marked reduction in the number of ganglion cells, severe neuronophagia, conspicuous gliosis, widened perivascular spaces and engorged blood vessels were noted throughout the basal ganglia. Neustaedter described 2 almost identical cases in which the striatum was bilaterally atrophic. The number of ganglion cells was reduced, and "partial degeneration" was present in the remaining cells. The red nuclei contained "pyknotic cells," and "considerable loss of

cells" was seen in the dentate nuclei and the molecular layer of the cerebellar cortex. The latter changes were also bilateral.

Bilateral destruction of the globus pallidus without concomitant neural lesions was described in 3 cases (Fischer; Scharapow and Tschernomordik [case 2]; Papez, Hertzman and Rundles). Destruction in these cases appeared to be the result of vascular disturbances. Papez, Hertzman and Rundles commented on the pathologic changes in their case, as follows [61]:

> There was almost complete absence bilaterally of the small lenticulostriate arteries, which normally arise from the first portion of the middle cerebral artery. Either the arteries had been pulled out at birth or, owing to other causes, had failed to develop in sufficient number.

The globus pallidus was in all cases bilaterally atrophic and deficient in ganglion cells. Papez, Hertzman and Rundles estimated that 75 per cent of the ganglion cells were absent in their case. Increases in glial nuclei and fibers were observed in all cases, as was reduction in the volume of pallidofugal fibers.

Status dysmyelinisatus of the globus pallidus, without coexisting or antecedent pathologic change elsewhere, was reported in 2 cases (Vogt and Vogt [case 20], Kreyenberg). The pathologic changes reported in these cases were bilateral and almost identical. In Weigert-stained sections the striopallidal fibers were described as pale and deficient in number. Both the internal and the external segment of the globus pallidus were reduced in volume. The myelin fibers within the pallidum were reduced in number and took the Weigert stain poorly. Pallidofugal fibers projecting to the lateral nuclei of the thalamus and the hypothalamus were similarly reduced in volume and poorly stained with the Weigert technic. The subthalamic nuclei (corpus Luysi) in both cases were described as "smaller than normal." Kreyenberg described the Nissl sections of the globus pallidus in his case as follows [59]:

> The ganglion cells in the pallidum were strikingly changed, especially in the caudal part. They were pale with indistinct borders and dark-staining dendrites. The glia was increased throughout and sometimes formed typical *Gliarasen*, with degenerative changes in the nuclei and pigmentation.

In 2 cases (Oppenheim and Vogt [case 1], Filiminoff) bilateral pathologic changes of the cerebral cortex were described. In the case reported by Oppenheim and Vogt the pathologic alterations were confined to the cortex and the underlying white substance. Abnormal smallness bilaterally of the central gyrus, the posterior portion of the lower frontal gyrus, the superior temporal gyrus and the adjacent parietal gyrus was described. The principal microscopic changes were reported in the precentral gyrus as follows [12]:

> There were normal order and disposition of the nerve cells with a preponderance of round cells, while the pyramidal cells were missing or very poorly developed and in abnormal positions.

Only occasional isolated giant pyramidal cells were reported in this area. Pronounced pathologic changes were described in the intracortical and subcortical white matter. These changes were described as follows [12]:

> One observed the myelin radiating *hirschgeweihartig* into the cortex, whereas in the normal brain it enters the cortex in the form of a broad lobe. Especially striking was the distribution of the intracortical myelin. Instead of the normal distribution, a formation suggestive of a *Fensterblumen* was present. It appeared as though the myelin had been compressed, distorted, displaced and separated into single shreds. Further, nests of gray substance of cortical origin were situated under the cortex.

Except for degeneration in the right lateral funiculus of the spinal cord, no other pathologic changes were noted.

In Filiminoff's case bilateral pathologic changes were described in the precentral gyrus and the striatum. By gross estimation, the thick-

TABLE 9.—*Chronology of 8 Reported Cases (Group 2) of Double Athetosis with Torsion Dystonia with Reference to Sex, Age at Onset, Age at Death and Cause of Death*

Author	Date	Sex	Age at Onset	Age at Death, Yr.	Cause of Death
Thomalla [74]	1918	M	13 yr.	14	Cirrhosis of liver
Westphal [75]	1919	M	42 yr.	43	Cirrhosis of liver
Richter [49] (p. 257)	1923	F	11 yr.	54	Cardiac failure
Laruelle and van Bogaert [69]	1929	F	Birth	9	Not reported
van Bogaert [65] (Case 3)	1929	F	2 yr.	10	Pulmonary tuberculosis
Ammosow [70]	1931	M	1 mo.	6	Accident
Meyer and Cook [71]	1935	F	2 (?)	16	Bronchitis and pulmonary congestion
Balthasar [72]	1939	F	Birth	5	Bronchopneumonia

ness of the precentral cortex was 25 per cent less than normal. *Ausfallen* of nerve cells was reported as conspicuous in the upper cortical layers, but the Betz cells and lower cortical laminas were preserved. In the striatum the number of small ganglion cells was significantly reduced.

Double Athetosis with Torsion Dystonia.—Clinical Manifestations: Eight cases of double athetosis with torsion dystonia were found which satisfied the criteria of this study (table 9). In 5 cases of double athetosis with torsion dystonia (Laruelle and van Bogaert,[69] van Bogaert [65] [case 3], Ammosow,[70] Meyer and Cook,[71] Balthasar [72])

69. Laruelle, L., and van Bogaert, L.: Étude anatomo-clinique d'un cas de syndrome rigide, avec spasme de torsion, Rev. neurol. **51**:941-948, 1929.

70. Ammosow, M. M.: Zur pathologischen Anatomie der pallidären Formen von Athetose, J. f. Psychol. u. Neurol. **41**:374-382, 1931.

71. Meyer, A., and Cook, L. C.: Etat Marbré, J. Neurol. & Psychopath. **16**:341-352, 1935.

72. Balthasar, K.: Ueber die Beteiligung des Globus pallidus bei Athetose und Paraballismus, Deutsche Ztschr. f. Nervenh. **148**:243-261, 1939.

symptoms appeared soon after birth or during infancy (table 9). Protracted labor in 1 case (Balthasar) was the only complication of birth noted. Birth was premature (at 7 months), but uncomplicated, in Ammosow's case. However, the infants were icteric shortly after birth in 2 cases (Laruelle and van Bogaert, Balthasar). In the remaining 3 cases onset of double athetosis with torsion dystonia occurred in the second and fourth decades of life. In these cases athetoid activity began insidiously and was not preceded by episodes of unconsciousness or sensory abnormality.

The initial symptoms were the same as those described in double athetosis without torsion dystonia. The abnormal motor activity involved the muscles of the tongue, face, neck, shoulder, torso and extremities. In 4 cases (Westphal,[73] Richter [49] [case 4], Thomalla,[74] Laruelle and van Bogart [69]) the athetoid activity was present in the tongue, face, neck, torso and proximal appendicular muscles. Thomalla stated [74]: "Athetoid movements in the fingers and toes were never observed." In the remaining 4 cases the athetoid activity in the extremities involved the distal appendicular musculature. The athetoid activity was similar to that previously described except for the involvement of the proximal appendicular muscles in the cases mentioned. The muscles of the neck, shoulder girdle, torso and pelvis exhibited gradually increasing tension and slowly twisted these regions into positions of extreme distortion. Such attacks lasted for variable periods and waned as the muscular spasm and accompanying torsion slowly diminished. During the attacks the head was drawn forward or backward, and the face was distorted in a painful grimace. Balthasar [72] described the attacks of torsion dystonia as follows:

> The vertebral column was slowly extended and turned to the right, so that the back was raised 10 cm. from the bed and for a minute produced an arc. With this hyperextension there was simultaneous twisting of the back to the right. This movement was involuntary and very slow, never jerky.

The muscles concerned with swallowing were affected in 4 cases (Thomalla, Westphal, Ammosow, Balthasar). Food was often retained in the mouth for long periods and frequently was regurgitated, sometimes in part through the nose. Smacking of the lips and noisy deglutition

73. Westphal, A.: Ueber doppelseitige Athetose und verwandte Krankheitszustande ("striäres Syndrome"): Ein Beitrag zur Lehre von den Lensenkernerkrankungen, Arch. f. Psychiat. **60**:361-400, 1919.

74. Thomalla, C.: Ein Fall von Torsionsspasmus mit Sektionsbefunde und seine Beziehungen zur Athetose double, Wilsonschen Krankheit und Pseudosclerose, Ztschr. f . d. ges. Neurol. u. Psychiat. **41**:311-341, 1918.

were common. Westphal [73] described this disturbance in his patient as follows:

> Swallowing and speaking were more and more disturbed, so that taking food was very difficult; especially was the swallowing of fluids disturbed, whereas masticated solid foods were swallowed better.

Balthasar's patient had great difficulty in swallowing and in learning to chew. Not until the patient was 5 or 6 years old did she learn to feed herself without assistance, and then she could take only fluids and puréed foods. Most of the difficulties in swallowing appeared to be due to involuntary spasm of the pharyngeal muscles.

According to Westphal and Ammosow, no paresis was demonstrable in their cases. Some degree of paresis, usually greatest in the lower extremities, was noted as present in 3 cases and was present by inference in the remaining 3 cases. Spasticity was present to some degree in all cases. In Thomalla's case increased resistance to passive movement was somewhat reduced during sleep but was still present. The extent of incapacitation of 3 patients (Ammosow; Meyer and Cook; Balthaar) was such that they could not sit, stand or walk. Muscular atrophy of the lower extremities was noted in Balthasar's case. Scoliosis, lordosis and kyphosis, with associated deformity of the thorax, were described by Richter, Westphal, and Meyer and Cook. Contractures of the elbow joints and of the knees were each reported once, while bilateral pes equinovarus was described in 3 cases. In 1 case (Thomalla) the patient complained of pain in the hand, forearm and frontal region of the head. No clinical evidence of sensory disturbance was found in these cases.

Slow, tedious, dysarthric speech, usually associated with exacerbation of athetoid and dystonic activity, was described in 6 cases. In several cases almost all sounds were incomprehensible, except to members of the patient's family. One patient was never able to speak (Laruelle and van Bogaert [69]). Balthasar's patient spoke only distorted monosyllables in a nasal monotone, which he described thus:

> She expressed her wishes in juvenile *telegrammstilhafter Weise,* in which she used only nouns, such as *"brot oder essen."*

Richter described the speech of his patient as initially loud, unpleasant and screeching and later explosive and inarticulate.

In 6 of the cases the patients were described as mentally defective. They were oriented for time and place. No disturbance of mood or affect was noted, and frank psychotic symptoms were not reported.

Pathologic Changes: Bilateral status marmoratus of the striatum (caudate nucleus and putamen) with coexisting or antecedent pathologic changes elsewhere was described in 2 cases (van Bogaert [case 3], Meyer and Cook) (table 10). Van Bogaert [65] reported bilateral *état*

marbré of the posterior and ventral portions of the putamen and of "almost the entire caudate nucleus," in association with pathologic changes in the precentral cortex. The fine myelin fibers in the striatum were similar to those previously described. In area 4 a clear "rarefaction" of Betz cells was described, together with "proliferation of neuroglia throughout layers V and VI of the cortex." In the case reported by Meyer and Cook a symmetric "marble state" in the dorsolateral parts of the putamen and in the internal portion of the caudate nucleus coexisted with "marked glial sclerosis" of the substantia nigra. They further described the pathologic changes of the striatum as follows [71]:

Holzer's stain revealed that the hypermyelinized areas corresponded entirely with the glial scars, and there was unmistakable evidence that these scars com-

TABLE 10.—*Location of Neural Lesions in 8 Reported Cases (Group 2) of Double Athetosis with Torsion Dystonia*

Author	Date	Location of Principal Lesion(s) (Bilateral)*	Sites of Other Lesions (Bilateral)*
Thomalla [74]	1918	Putamen	
Westphal [73]	1919	Putamen	
Richter [49] (p. 257)	1923	Striatum	Substantia innominata; substantia nigra
Laruelle and van Bogaert [69]	1929	Globus pallidus (status dysmyelinisatus)	
van Bogaert [65] (Case 3)	1929	Striatum †	Precentral cortex
Ammosow [70]	1931	Globus pallidus (status dysmyelinisatus)	
Meyer and Cook [71]	1935	Striatum †	Substantia nigra
Balthasar [72]	1939	Globus pallidus (status dysmyelinisatus)	

* All lesions were bilateral.
† Status marmoratus.

pletely covered the field taken by the hypermyelinized foci. In many parts of the affected areas the ganglion cells had disappeared.

The myelin fibers (Weigert stain) in the striatum were described as "intertwined" and "dense," but were usually "delicate" and showed "frequent thickenings and end-bulbs."

Bilateral destruction in the putamen by necrotizing vascular lesions, without noteworthy coexisting or antecedent pathologic changes elsewhere, was described in 2 of these 8 cases of double athetosis with torsion dystonia (Thomalla, Westphal). Richter (case 4) described multiple small necrotizing vascular lesions in the posterior portions of the putamen, the substantia innominata and the substantia nigra which he believed corresponded with *état fibreux*, as described by the Vogts. A noticeable deficit of striopallidal fibers and of myelin fibers within

the pallidum was reported. The pallidofugal fibers were recorded as normal, but the volumes of the subthalamic nuclei were reported as "noticeably diminished."

Bilateral status dysmyelinisatus of the globus pallidus, without coexisting or antecedent pathologic changes elsewhere, was described in 3 of these 8 cases by Laruelle and van Bogaert, Ammosow and Balthasar. The pathologic alterations in these cases were similar to those reported by Vogt and Vogt (case 20) and Kreyenberg (page 18, copy).

Hepatolenticular degeneration was considered a possibility by two authors (Thomalla, Westphal) in cases of striatal destruction associated with cirrhosis of the liver (table 9). Both, however, concluded that the pathologic change in the liver was "probably a developmental defect."

Miscellaneous Clinicopathologic Cases.—Many cases might have been included with the 42 cases studied were it not for the inadequacies in the clinical descriptions or pathologic reports. Most of the cases of *état marbré* described by the Vogts [28] (1920) belong to this group. Four cases of double athetosis were reported by Alexander [24] in which certain histologic aspects of the pathologic changes were treated in detail, but none of the reports was complete.

In several cases, status marmoratus of the striatum has been described, but athetoid activity was not present or was not described. Case [75] recorded an instance of status marmoratus of the striatum coexisting with cortical demyelination, cell destruction and glial scars. The patient was thought to have had encephalitis; athetoid activity was not reported. No athetoid activity was described by Juba [76] in a case in which autopsy revealed hydrocephalus, bilateral atrophy of the thalamus, atrophy of the right dentate nucleus, almost complete absence of the corticospinal and corticopontile tracts bilaterally and status marmoratus of the striatum. Norman [77] reported status marmoratus of the putamen and precentral, parietal and occipital cortex bilaterally, although athetoid activity was never seen. The author attributed the absence of athetoid movement to coincident damage to the precentral cortex. Löwenburg and Malamud [78] described 2 cases of status marmoratus of the striatum and thalamus but did not report athetoid activity.

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75. Case, T. J.: Status Marmoratus Related to Early Encephalitis, Arch. Neurol. & Psychiat. **31**:817-823 (April) 1934.

76. Juba, A.: Ueber eine frühinfantile Grosshirnmissbildung (Polyporencephalie und Status marmoratus), Ztschr. f. d. ges. Neurol. u. Psychiat. **157**:622-635, 1937.

77. Norman, R. M.: An Example of Status Marmoratus of the Cerebral Cortex, J. Neurol. & Psychiat. **1**:7-12, 1938.

78. Löwenburg, K., and Malamud, W.: Status Marmoratus: Etiology and Manner of Development, Arch. Neurol. & Psychiat. **29**:104-124 (Jan.) 1933.

Norman [79] later reported a case of "état marbré of the thalamus following birth injury," but stated that athetoid activity was not observed.

Nielsen and Ives [80] described a case of athetoid activity in all extremities which was present from birth and was accompanied with spasticity. Except for a small "patch of microgyria in the parietal regions" and slight "deposition of pigment in the subpial cells" of the premotor cortex, no gross or microscopic pathologic changes were reported.

SUMMARY AND CONCLUSIONS

A review of the literature disclosed the reports of 42 cases of hemiathetosis, double athetosis and double athetosis with torsion dystonia with adequate clinical descriptions and reports of pathologic changes. Analysis of these cases led to the following conclusions:

1. Athetosis is a pattern of involuntary dyskinesia which can be distinguished from chorea and is characterized by increases and decreases of tone in irregular sequence in antagonistic muscle groups and slow involuntary movements involving chiefly, but not exclusively, the distal appendicular musculature such that vermicular activity results.

2. Hemiathetosis usually develops after hemiparesis, or in association with it, as a consequence of necrotizing cerebrovascular lesions which destroy part of the internal capsule and striatum on the side opposite that of the activity. In some cases hemiathetosis may result from cerebrovascular lesions located in the diencephalic course of the brachium conjunctivum and in the region of the subthalamic nucleus, contralateral to the activity.

3. Hemiathetoid activity may be present despite secondary degeneration of the corticospinal tract on the affected side, but cases are rare.

4. Double athetosis usually manifests itself in early infancy, and in almost half the cases (46 per cent) a history of trauma at birth is recorded. Bilateral paresis and spasticity, particularly of the lower extremities, are present in almost one-half the cases of double athetosis. Retarded speech development and/or dysarthria are present in a high proportion (80 per cent) of the cases, and more than half (58 per cent) of the patients are mentally defective.

5. Double athetosis is most frequently a consequence of bilateral status marmoratus (*état marbré*) of the striatum, but also appears as a result of bilateral necrotizing cerebrovascular lesions in the striatum.

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79. Norman, R. M.: État Marbré of the Thalamus Following Birth Injury, Brain **72**:83-88, 1949.

80. Nielsen, J. M., and Ives, E. R.: Double Athetosis Without Status Marmoratus, Bull. Los Angeles Neurol. Soc. **2**:72-77, 1937.

6. Double athetosis may appear as a result of bilateral status dysmyelinisatus of the globus pallidus or of localized destruction in the globus pallidus bilaterally.

7. Status marmoratus of the striatum does not inevitably result in double athetosis, although such instances are rare.

8. Double athetosis may appear without demonstrable pathologic change in the striatum or globus pallidus, but such cases are rare.

9. Double athetosis with torsion dystonia usually manifests itself in infancy but may appear later in life. The incidence of paresis, spasticity, speech disturbances and mental impairment is the same as that in double athetosis without torsion dystonia.

10. Double athetosis with torsion dystonia is a consequence of the same pathologic changes in the same structures as those reported in cases of double athetosis without torsion dystonia.

Adequate clinical descriptions and pathologic study will continue to be of value in elucidating the genesis and nature of these phenomena, particularly when supplemented with cinematographic records.

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OPHTHALMOPLEGIC MIGRAINE

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SINCE the first description of ophthalmoplegic migraine, neurologists have been divided into two groups with regard to the nosologic standing of the disease. One group, with Charcot, consider this clinical syndrome a common migraine complicated in some of its attacks with ophthalmoplegia; the other group, with Möbius, consider it a relapsing ophthalmoplegia accompanied with cephalalgia and vomiting, a condition quite distinct from migraine.

As a result of the many cases that have been studied and the better knowledge of the migrainous syndrome in general, it is possible to form a more informed opinion of the question, which, according to Charcot, "is, and will perhaps long remain, under study." It is to this revision that I wish to contribute by bringing my observations on the cases of ophthalmoplegic migraine which I have had the opportunity of studying during the past twelve years. Their study leads to certain pathogenic considerations, and particularly to a conclusion concerned with the treatment of the disorder which to date has had no firm sanction.

I wish first to present 7 cases of ophthalmoplegic migraine which appeared on a background free from any previous migrainous manifestations, either personal or hereditary.

REPORT OF CASES

CASE 1.—A man aged 44, with no history of migraine, either personal or hereditary, or of syphilis, on Aug. 15, 1941 was seized with hemicrania (left side), the attack lasting about two hours. These seizures recurred three times a week and were the first the patient had ever experienced. There was no accompanying nausea or vomiting. During September and October the attacks became more violent and occurred more frequently. On October 17, during a more violent attack, he had diffuse myalgia. The following day, on his waking, diplopia appeared and remained even after the disappearance of the hemicrania. On October 28, the diplopia still persisting, the hemicrania recurred on the left side and was very violent.

Spinal puncture revealed 0.35 Gm. of albumin and 0.45 Gm. of sugar, per hundred cubic centimeters, and 2 white cells per cubic millimeter; the Pandy and Nonne-Apelt tests gave negative reactions for globulin, and the reaction to the Wassermann test was negative.

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During November the pain and diplopia were still intense. In December the patient was still in bed, and the headaches were more violent in the temporal region, but the severity diminished at times. The reflexes were normal. The left sixth cranial nerve was paralyzed. The pupils reacted normally in accommodation and to light. Another examination of the spinal fluid revealed 3 Gm. of albumin per hundred cubic centimeters; 10 lymphocytes per cubic millimeter; a positive reaction to the Nonne-Apelt test and a negative reaction to the Pandy test for globulin, and a negative Wassermann reaction. The urine was normal. Roentgenograms of the skull showed no abnormality.

Intravenous administration of salicylates and diathermy were tried, with poor results. Under roentgen treatment the headaches diminished gradually. The patient was discharged on Jan. 28, 1942, completely cured. Unfortunately, he refused to have another spinal puncture.

In this case, with no history of migraine, either personal or hereditary, hemicrania (left side), of unknown cause, appeared and recurred frequently during a period of two months. At the end of this time an attack, accompanied with myalgia, terminated in paralysis of the left sixth cranial nerve. Thus, the clinical picture of ophthalmoplegic migraine became complete. The pain later disappeared, but the paralysis persisted. The pathologic process seemed to be clearing, and we were awaiting its end, with restoration of the sixth cranial nerve, according to the classic pattern. On the contrary, a renewal of the process was taking place, and the pain reappeared in more violent form. The spinal fluid examined at that time was normal. During the next two months the clinical situation became aggravated, the diagnosis being confirmed by another examination of the spinal fluid, which showed 3 Gm. of albumin. This state continued for two months, but recovery followed roentgen therapy directed to the pontile area.

On the whole, the impression is that of a process of progressive development due to a humoral disturbance of exudative character.

Case 2.—A woman aged 32 had no history of migraine, either personal or hereditary, or of syphilis. On March 10, 1938 migraine appeared, the pain being severer on the left side. Slight at first, it became more intense day by day. On the eighth day nausea and vomiting appeared, and on the twelfth day, diplopia. Vomiting and diplopia disappeared on the sixteenth day, and the migraine was less severe but was intense for an hour or two each day.

The reflexes were normal; the pupils reacted normally to light and in accommodation. The blood pressure was 170 systolic and 90 diastolic. The urine was normal.

Studies of the blood revealed 0.42 Gm. of urea, 0.88 Gm. of sugar and 2 Gm. of cholesterol, per hundred cubic centimeters; 4,200,000 red cells, and 7,000 leukocytes, with a normal formula. The Wassermann reaction was negative.

Examination of the spinal fluid showed 0.50 Gm. of protein and 0.52 Gm. of sugar per hundred cubic centimeters, a negative Wassermann reaction, a positive Pandy reaction for globulin and 3 cells per cubic millimeter. A roentgenogram of the skull revealed nothing significant.

The patient was discharged in the early part of May, completely cured.

She returned to the hospital on November 1, complaining of headaches, which had had their onset a month previously, without nausea or vomiting. Objectively, the examination revealed nothing pathologic. The migraine disappeared after a month but reappeared from time to time for a short period. The blood pressure remained constant.

In this case, without any history of a similar condition, after progressive development, the ophthalmoplegia disappeared in a few days, whereas the migrainous element persisted a month longer and reappeared in successive attacks thereafter. The increase of protein in the spinal fluid is to be emphasized, as well as the hypertension, in this case, in which a migrainous habit had been created.

Case 3.—A patient aged 45, with no migrainous antecedents or history of syphilis, in 1931 had onset of pain on the right side of the forehead, just above the eyebrow. Diplopia and ptosis of the right eyelid appeared on the third day after onset of the headache. This state lasted two months and then disappeared gradually.

On Sept. 28, 1936 pain in the right frontal area with diplopia and ptosis of the right eyelid reappeared. This state continued until November 19, when the patient entered the hospital. There was no vomiting, nausea or pyrexia. The pupils reacted normally in accommodation and to light. There were still ptosis and paralysis of the internal and inferior rectus muscles on the right side. The reflexes and ophthalmoscopic findings were normal. The roentgenograms of the skull revealed no abnormality. The spinal fluid and blood were normal, and the Wassermann reaction was negative.

The patient left the hospital in December, after treatment with salicylates.

In this case, again, without similarly affected antecedents, ophthalmoplegic migraine appeared and cleared in two months. However, after five years without symptoms, the condition reappeared, with the same symptoms but of longer duration (four months), the recurrence disclosing the establishment of a migrainous habit heretofore absent in the personal and familial history of the patient.

Case 4.—A patient aged 25, with no history of migraine, either personal or hereditary, or of syphilis, in July 1938 was seized with headaches in the left frontal region, of three weeks' duration. In April 1939 the headache recurred, with ptosis of the left eyelid. The patient recovered in a week. In May he had diplopia on looking to the left. In June, the diplopia persisting, the headaches in the left frontal area reappeared, and the entire syndrome persisted until the patient entered the hospital, on August 28.

On admission the patient had violent headaches in the left frontal area with exacerbations. The left fourth cranial nerve was paralyzed. The pupils were normal and reacted in accommodation and to light. The deep and cutaneous reflexes were normal.

Examination of the spinal fluid revealed 0.50 Gm. of protein per hundred cubic centimeters, negative reactions to the Nonne-Apelt and Pandy tests for globulin, a negative Wassermann reaction and 5 cells per cubic millimeter.

The urine was normal; the blood picture was normal; the Wassermann reaction of the blood was negative. A roentgenogram of the skull showed no abnormality. This state continued without modification.

On September 7, a febrile condition developed, with a temperature of 103.1 F., which proved to be typhoid. The Widal reaction was positive in a 1:2,000 dilution. After the sixth day of this febrile state the headaches began to diminish, together with the diplopia. By September 22 the ophthalmoplegic migraine had disappeared, the typhoid continuing on its course.

In this case, the following points are significant: (1) the previous appearance (ten months before) of a long-lasting, simple migraine on the same side as the subsequent ophthalmoplegic migraine; (2) the change in the nerve involved in the successive seizures (from the third to the fourth cranial nerve); (3) the appearance of the ophthalmoplegia a month prior to the migraine in the course of the third attack; (4) the slight modification of the spinal fluid; (5) the impression of the creation of a migrainous habit, the process being located in two successive cranial nerves.

The most interesting feature of this case was the therapeutic effect of the incidental febrile occurrence, which abolished the ophthalmoplegia and the constant pains which had been present for three months.

CASE 5.—A man aged 40, with no history of migraine, personal or hereditary, or of syphilis, during the night of Jan. 8, 1942 was seized with a violent headache. The following morning diplopia, nausea and sialorrhea occurred. This condition continued, and on the sixth day the pain became localized in the frontoparietal area and the left eye. A low grade fever was noted. This painful state continued without modification, and the patient entered the hospital on February 28.

Examination.—Paralysis of the left sixth cranial nerve was noted. Ophthalmoscopic examination revealed nothing abnormal. The pupils reacted in accommodation and to light. The deep and cutaneous reflexes were normal.

Blood Picture: The cell counts and formula were normal; the urea measured 0.25 Gm. per hundred cubic centimeters; the Wassermann reaction was negative.

Spinal Fluid: The protein measured 0.20 Gm. per hundred cubic centimeters; the cell count was 2 per cubic millimeter; the reactions to the Nonne-Apelt and Pandy tests for globulin were negative; tension was 16 mm. before and 9 mm. after withdrawal of spinal fluid (Claude manometer).

Roentgenograms of the skull revealed nothing abnormal.

Course.—In spite of diathermy, roentgen therapy and administration of salicylates, the pain and the diplopia continued night and day during March, April and May. On March 6, after a subcutaneous injection in the arm, an inflammatory process (phlegmon) appeared, with chills and increased temperature (104 F.). On the fourth day of this state, the migraine had almost disappeared, and the diplopia was notably improved. A few days later, when the abscess was incised, the temperature fell to 100.4 F.; the migraine had disappeared completely, and the diplopia cleared two days later.

The patient, when seen again in August 1945, stated that the headaches had not reappeared

Three features are to be emphasized in this case: (1) the abruptness of establishment of the syndrome, in one night; (2) the violence of the pain, which, generalized in its first appearance, was localized later on the paralyzed side, and (3) the presence of a low grade fever, a general symptom to be compared with the diffuse myalgia in case 1. But.

far above all these features, this case has been instructive because of the beneficial effect on the course of the ophthalmoplegic migraine of the incidental febrile state produced by the inflammatory process, an observation corroborating the similar conclusion in case 4.

CASE 6.—Anast., aged 43, had no history of migraine, either personal or hereditary, or of syphilis. The father had had multiple sclerosis.

In 1929 the patient had onset of migraine on the right side, which became increasingly intense. On the sixth day after onset paralysis of the right sixth cranial nerve appeared. The spinal fluid was found to be normal in all aspects. On the eighth day the pain became unbearable, and the patient complained of numerous extrasystoles, which were easily detected. After the tenth day slight improvement was noted, and a month later the patient was discharged as cured. For the next ten years there was no recurrence of the migraine.

In September 1939 migraine reappeared on the same side as before. The pain became more intense, and on the sixth day diplopia and extrasystoles were noted. On November 24 the patient entered the hospital, complaining of the same symptoms.

Examination on admission revealed paralysis of the right sixth cranial nerve. The optic disk was normal. The pupils reacted equally in accommodation and to light. The deep and cutaneous reflexes were normal. The urine was normal.

The blood picture was normal, with 0.20 Gm. of urea and 0.95 Gm. of sugar per hundred cubic centimeters and a negative Wassermann reaction.

Examination of the spinal fluid showed 0.25 Gm. of albumin per hundred cubic centimeters, 1 cell per cubic millimeter and negative reactions for globulin in the Nonne-Apelt and Pandy tests. Examination of the heart revealed extrasystoles. On December 29 the patient was discharged, fully recovered.

In May 1941 migraine appeared on the left side, with paralysis of the left sixth cranial nerve. The headache continued, and in June paralysis of the left facial nerve, accompanied with hypesthesia of the left side of the face, appeared. Within thirty days all the symptoms disappeared, and the patient left the hospital, free from symptoms.

During November migraine (left side) appeared, with paralysis of the left superior rectus muscle and numerous extrasystoles.

Again, in this case, without any previous history of migraine, ophthalmoplegic migraine with paralysis of the right sixth cranial nerve appeared, with recovery in one month. This incident had been forgotten, and ten years later an attack identical with the previous one, but of severer degree, occurred. One forms the impression that the habit was well fixed in the central nervous system; yet, after a symptom-free period, of shorter duration than before, a new attack of ophthalmoplegic migraine occurred on the opposite side, involving the opposite sixth nerve, after which the process extended to nonophthalmic nerves, the seventh and fifth cranial, on the same side, the pathologic process always involving structures at the pontile level. Recovery occurred in three months, but the condition reappeared after three months on the left side, involving another nerve, the third, and extending to the peduncular area.

In addition, one must point out the presence of extrasystoles, which accompanied each attack of ophthalmoplegic migraine, whichever the side of involvement, and disappeared with the migraine, implying the involvement of the vagus nerve in the pathologic process.

CASE 7.—Kar., aged 35, with no history of migraine, personal or hereditary, and no history of syphilis, in September 1943, after domestic worries and several sleepless nights, had onset of diplopia, due to paralysis of the left sixth cranial nerve, without headache. Fifteen days later hemicrania appeared on the left side, with daily exacerbations but no vomiting. This state continued through November, December, January and February. In March 1944 the hemicrania disappeared, but the diplopia continued until May. In September 1944 the hemicrania reappeared on the left side, without diplopia but with suppression of the lacrimal and nasal secretions on that side. The deep, cutaneous and pupillary reflexes were normal; ophthalmoscopic studies and roentgenograms of the skull revealed nothing abnormal. Through October, November and December 1944 this state continued unchanged.

During January and February 1945 the hemicrania became more violent. Since March 7 paralysis of the left sixth cranial nerve had been present, the deep, cutaneous and pupillary reflexes and the temperature being normal. In April the lacrimal and nasal secretions became normal. In May the hemicrania and diplopia improved, and in June the patient was completely recovered. In 1947 the patient was found to be in good health.

In this case, without any migrainous antecedents, the ophthalmoplegic migraine occurred after a psychic trauma, which at first disturbed sleep. Here, again, the paralysis preceded the hemicrania. The second attack, localized on the same side, was not accompanied with paralysis, but was associated with a neurovegetative disturbance (suppression of the lacrimonasal secretions), implying the participation of the lacrimonasal nucleus, located in the pontobulbar boundary near the inferior extremity of the nucleus of the seventh cranial nerve. This condition continued five months, at which time the paralysis of the left sixth cranial nerve completed the clinical picture. This disappeared after four months of hemicrania, recovery being noted only after the return of the lacrimonasal secretion.

This case was interesting because of the duration of the attacks, the participation of the neurovegetative nucleus and the appearance of the process after psychic trauma.

What comment may one make on these cases of ophthalmoplegic migraine in subjects without migrainous antecedents?

1. These attacks were generally more prolonged than in ordinary migraine, the difference not being absolute, since some attacks have been of only a few days' duration and others resembling the classic migraine, of long duration.

2. Except for a case in which the condition followed a psychic trauma, it was not possible to determine the cause of the attacks.

3. The pains were particularly violent and generally progressive, increasing each day to a degree which was maintained for a long period, although in some cases the onset was acute and striking. The pain was unilateral, except in a case in which, after being general, it became localized, this change being explained by a mechanism of irradiation from the focus of the processes considered here.

4. The pain was often accompanied with nausea and vomiting, without this being the general rule.

5. The paralysis presented only one characteristic, that of being localized on the same side as the pain. In other respects it presented variations. Although in general, and in accordance with the classic type, the paralysis appeared several days, or several weeks, after the onset of pain, it has been observed to become established at the same time, and in 2 cases it preceded the pain from two to several weeks, so that in the first phase the condition seemed to be simple paralysis of a cranial nerve. The paralysis affected oftener one of the oculomotor nerves (third, fourth or sixth), but the nerve affected was not necessarily the same with repeated attacks, whatever the classic description may say. I have seen it change from one nerve to another after an attack. Other nerves than the oculomotor were affected, such as a motor (seventh), sensory (fifth or eighth) or vegetative (tenth, nucleus lacrimonosalis) nerve, but always nerves the nuclei of which were located in the peduncle, the pons or the medulla oblongata.

6. Over and above the variation in the nerves affected, one must remark the variation in the affected side, a feature equally opposed to the classic description, the migraine changing, in rare cases it is true, the side of localization in successive attacks.

7. The spinal fluid was frequently altered (hyperalbuminosis, lymphocytosis).

After the study of cases of ophthalmoplegic migraine occurring on a background free of migrainous antecedents, I shall now discuss the disturbance in cases with a history of migraine.

Case 8.—Since the age of 30, the patient had had attacks of simple migraine on the left side, occurring twice a month, without vomiting and lasting an average of two days. Ten years prior to admission, the patient had had an attack of migraine on the right side, lasting a week and accompanied with paralysis of the right facial nerve, which disappeared a month later. After that the usual attacks occurred, but ten days before the patient's admission migraine, which was very severe, appeared with diplopia and paralysis of the left sixth cranial nerve. This condition was still present when the patient entered the hospital.

Examination revealed that the optic disk, pupillary reflexes and deep and cutaneous reflexes were normal. The Wassermann reaction of the blood was negative. Studies of the spinal fluid revealed 0.040 Gm. of protein per hundred cubic centimeters, 2 cells per cubic millimeter, a slightly positive Pandy reaction for globulin and a negative Wassermann reaction.

After a duration of two months, the symptoms disappeared in a few days.

Thus, in this case of ophthalmoplegic migraine, occurring on a migrainous background, one encountered, as in the previous cases, the change in the side involved and the variation in the affected nerve, as well as the slight alteration in the spinal fluid.

CASE 9.—Fot., aged 32, had attacks of migraine two or three times a month; these consisted in a feeling of constriction in the temporal regions and lasted two to three hours. In July 1944 she had a sudden, strong emotional experience. Knowing that the Germans had executed persons in her village, she asked her people to live with her in order that she might shelter them. On meeting her people and seeing that her brother was not with them, she thought that the Germans had executed him. One of the members of the family informed her that he had only been arrested, but her grief and anxiety for her brother were intense. That day she began to suffer violent pains in the frontal region and was confined to bed. Fifteen days later the condition became aggravated, with nausea, vomiting and diplopia. When the patient was examined during the latter part of August, the condition was still present, together with paralysis of the left sixth cranial nerve. The optic disks and the pupillary, cutaneous and deep reflexes were within normal limits. The blood pressure was 130 systolic and 70 diastolic, and the Wassermann reaction was negative.

At the end of November the diplopia disappeared, and the severity of the hemicrania was greatly reduced. By the middle of December she had fully recovered; but on April 18, 1945 the patient, after another psychic trauma, had become affected by a vertiginous state, with numerous attacks of vomiting. These episodes were so grave that she was confined to bed, but recovered in twenty days.

In this case, the classic migraine, after a psychic shock, had been transformed into a violent ophthalmoplegic form, affecting the sixth cranial nerve and lasting five months. A similar condition occurred five months later, after another psychic incident, but to a slighter degree and affecting another cranial nerve, this time the vestibular.

CASE 10.—Ya., aged 35, had for a number of years had typical migraine with hemicrania (left side), nausea and vomiting. On March 15, 1945 the patient was stung by a wasp just outside the left eye. The eyelid and cheek became edematous, and the pain was severe. From that moment she experienced severe hemicrania on the left side, and after a week diplopia developed.

On her admission to the hospital, examination revealed paralysis of the left sixth cranial nerve and hypesthesia of the cutaneous areas corresponding to the superior and middle branches of the fifth cranial nerve of the same side. The hemicrania continued, and the temperature was 99.5 F. for one day.

Laboratory examination revealed a normal blood count and formula. The urea was 0.50 Gm. per hundred cubic centimeters. The Wassermann reaction was negative. The protein of the spinal fluid measured 0.20 Gm. per hundred cubic centimeters; the cell count was 7 per cubic millimeter; the Wassermann reaction was negative. All reflexes were within normal limits.

The edema of the cheek disappeared a few days later, and the hemicrania was less severe. On April 23 the paralysis of the sixth cranial nerve was still present, but to a slighter degree, as was the hypesthesia of the fifth cranial nerve. By June 22 the patient had fully recovered. She had had no complaint since, except for slight attacks of migraine, once a quarter, when, at the beginning of January

1949, she underwent a strong psychic trauma. In the course of military operations in the area where she lived, the authorities were obliged to proceed to numerous arrests on suspicion. Among the persons detained was the patient, who had to remain in prison for a month. Her distress was great. She felt afflicted at being in prison, offended in her honor, in her dignity, and indignant at the injustice suffered, for she had never dabbled in politics and, above all, had never acted contrary to the authority of the state. This month lived in prison had been for her a time of atrocity and acute moral pain, which was not effaced either by her release or by the recognition of her innocence. Several days after her incarceration violent hemicrania appeared on the right side, accompanied with vomiting and, five days after, with diplopia, internal strabismus of the right eyeball, paralysis of the right sixth cranial nerve and hypesthesia in the area of the right fifth cranial nerve. This state persisted through February.

At the beginning of March, when the patient came under my observation, she was confined to bed, her pain diminishing at times but coming back in more violent form, to reach an unbearable degree, and accompanied then with violent vomiting. The internal strabismus was at its maximum, and the hypesthesia (touch, pain and temperature sense) of the right trigeminal area was pronounced. The temperature was normal. Pyretotherapy was then instituted. Although the patient's febrile reaction was slight, her temperature never exceeding 100.4 F. after each injection, the migraine, as well as the vomiting, disappeared after the third febrile reaction; the hypesthesia of the fifth cranial nerve began to improve, and the strabismus became slighter. Unfortunately, she had been compelled to return to the village because one of her children was ill. In spite of the brevity and the slightness of the pyretotherapy, one month after her departure the patient was without pain at any time and the strabismus was becoming increasingly less.

In this case, a patient who was already subject to attacks of migraine experienced, on the sting of a wasp, local edema and slight fever; an attack of ophthalmoplegic migraine occurred on the side of the old migraine, accompanied with a slight lymphocytic reaction of the spinal fluid. More than three and a half years later, after a psychic trauma, a new attack of ophthalmoplegic migraine appeared, involving the fifth and sixth nerves but affecting the opposite side.

In this case, the first attack appears to support the toxic theory, or, to be more exact, the allergic theory, of pathogenicity of the migraine. The second attack, however, appearing after a psychic trauma and resembling in all particulars the first except for the side concerned, appears to be of exceptional interest, without refuting the hypothesis of an allergic pathogenesis, the appearance of allergic manifestations after psychic episodes being well known.

Comment.—After studying these cases, one forms the opinion that these attacks of ophthalmoplegic migraine represent only the augmentation and extension of the ordinary migrainous process and that all the comments on the condition which occurs on a nonmigrainous basis can be repeated here. Except for the absence of previous attacks of migraine, there is no difference between the two forms of ophthalmoplegic migraine.

With regard to the pathogenesis of the disorder, the vasomotor mechanism meets with unanimous approval. It is satisfying with regard to the acute onset, such as that in case 2; but when the clinical picture is not too acute in development, the pain becoming severer with time, followed by the paralysis, the vasomotor theory does not seem very convincing. Indeed, it is possible to postulate a vasoconstriction reaching its maximum progressively which, by the decrease of the blood supply, will produce trophic changes in the cells of the affected nuclei, changes generally reversible with the reestablishment of the normal blood supply after the end of the vascular spasm. Such a mechanism, perfectly conceivable, seems, nevertheless, "made to order" to explain the circumstances and is inadequate to account for the change in the spinal fluid encountered in some cases (hyperalbuminosis; lymphocytosis).

In these cases an exudative mechanism must be added to the vascular —the *seröse Entzündung* type (Rössle), that is, an alteration in the physiologic permeability which takes place in the interstitial spaces of the smooth meninx and the spaces of the neighboring nerve tissue integrated in the same circulatory area, an explanation similar to Kammerer's theory of the migrainous syndrome. In addition to the pain, the consequence of this disturbance in permeability is, for the meninx, the hyperalbuminosis, and even the lymphocytosis, of the spinal fluid and, for the nerve tissue, the anatomic alteration of the nerve cells of the nuclei of the cranial nerves affected, the cells being drowned in a tide of albuminous fluid, which disturbs their nutritional processes. Under such conditions, it is understandable that the spontaneous recovery of the whole process may be very slow and that, this process having once taken place, a locus minoris resistentiae will be created at that point, favoring future repetition.

Charcot, on the basis of a case of ophthalmoplegic migraine in which autopsy showed that the root of the common oculomotor nerve was surrounded by an abundant exudation, with thickening of the pia mater at this point, stated:

> . . . It is only with the repetition of the attacks that purely dynamic and temporary changes left after them a "thorn," a *point d' appel,* a locus minoris resistentiae, on which were fixed the neoplastic products, preferably under the influence of the diathesic state, and independent of the migrainous disorder.

As I have just said, I believe that in many cases the condition can be interpreted in such a manner when the successive attacks always affect the same nerve; but in the case of Charcot the opposite explanation could be upheld—an inflammatory lesion produced by an unknown cause, prior to the migraine, serving as a point of irritation, and so creating the ophthalmoplegic migraine, or at least its localization at this point.

The cases next to be described argue in favor of such a concept.

CASE 11.—M. H., in 1929, a year after her birth, was stricken with poliomyelitis during an epidemic and remained for five days in a comatous state, with elevation of temperature to 104 F. When she regained consciousness, she was unable to keep her eyes open. When this stage was over, she again was able to keep her eyes open, but right strabismus had developed. The child then began to have violent headaches, and when she grew up the migraine was localized to the right side.

In 1933, while under my care, she had true hemicrania (right side) with partial paralysis of the right third cranial nerve. Examination of the spinal fluid revealed 0.36 Gm. of protein and 0.70 Gm. of sugar per hundred cubic centimeters and 1 cell per cubic millimeter, with negative reactions to the Nonne-Apelt and Pandy tests and a negative Wassermann reaction.

In March 1943 she returned with the complaint of migraine on the right side, which had never ceased and which occurred every month. She described the pain as occurring around the right orbit and extending to the homolateral temporal region, lasting for a few hours and accompanied with violent vomiting. Objectively, paralysis of the right elevator palpebrae and right superior rectus and internal rectus muscles was noted, with diminished reaction of the pupil to light. The tendon reflexes were within normal limits. The strabismus seemed to become severer during the course of the migraine attack.

When I again saw the patient, on April 9, 1946, the attacks of migraine had continued to occur but were less severe.

In this case an inflammatory process (poliomyelitis) had produced an indelible lesion on the nucleus of the third cranial nerve. The migrainous attacks which had occurred since started from this point and were ophthalmoplegic in type, since they were always accompanied with an accentuation of the residual ocular paralysis. The role of preexisting organic changes as the *point d' appel* is obvious; but it may be stated that not only does the lesion act as "point of call," thus localizing the migrainous attacks, but it creates the migrainous habit, since in this case the condition began to manifest itself as soon as the lesion was formed, at the age of 1 year, at an age when the migraine, whether ophthalmoplegic or not, had been observed.

CASE 12.—Con., aged 23, with no migrainous antecedents in the family and no history of syphilis, at the age of 6 years, during an epidemic of poliomyelitis, had a febrile illness for three days, accompanied with ptosis of the left eyelid and deviation of the globe outside the midline. After three weeks the patient recovered, but the ptosis and strabismus had continued, though to a less degree.

Some months later hemicrania appeared, with recurrence of the attacks about twice a month. The pain involved the left temporal and orbital regions, with nausea and vomiting. During this time the ptosis and strabismus became more intense. Five or six times a year the attack of migraine lasted three days, the ptosis and strabismus becoming increasingly intense and lasting three days longer than the migraine. At times the attacks of migraine would last a week and the vomiting be very severe. The deviation of the eye would reach the external angle of the palpebral fissure. On these events, the paralytic phenomena were prolonged for three weeks and then returned to normal. I saw the patient ten days after such

a severe attack. The ptosis was of moderate intensity, and the course of the globe inward and upward was very slight. The pupils were greatly dilated and did not react in accommodation or to light. The cutaneous and deep reflexes were within normal limits.

CASE 13.—Gl., aged 19, with no migrainous antecedents in the family, in 1934, when he was 6 years old, had a febrile disease, with a temperature of 104 F. He had violent headaches, predominating on the right side, with vomiting throughout the entire period, of ten days. The child recovered but had since had attacks of hemicrania on the right side, beginning at the periorbital region and radiating to the occipital region, accompanied with vomiting, which lasted from three to four days. These symptoms would recur after a remission of three or four weeks. This state continued, and in October 1946, during an attack, there appeared paralysis of the right eyelid (ptosis), which became total in two days, accompanied with diplopia. Five days after the onset the hemicrania disappeared, but the ophthalmoplegia continued, the ptosis improving slightly. Since then the attacks had occurred periodically, the ptosis becoming severer with each attack, and the diplopia remained. In May 1947, when we examined the patient, we observed medium ptosis of the right eyelid, total paralysis of the movements of the right eyeball upward, downward and inward, mydriasis and loss of pupillary reflexes to light and in accommodation.

The neurologic condition was normal. The Wassermann reaction was negative. Studies of the spinal fluid showed 1 cell per cubic millimeter, 0.30 Gm. of protein and a negative Wassermann reaction.

In this case, there was not, as in the previous cases, the ocular paralysis as proof of the organic lesion of the first infectious attack. Nevertheless, the long infectious incident in a child without migrainous antecedents, accompanied with severe headaches and vomiting, can be interpreted with great probability as a local meningeal reaction to an unknown infection. This infection, after the child's recovery, must have left somewhere near the roots of the right third cranial nerve a slight meningeal change as an irritative "thorn," the cause of the establishment of the migrainous habit. The extension of the process from the meningeal vascular area during one of the attacks brought the vasomotor anomaly to the underlying nerve tissue near the nucleus of the third cranial nerve. Unfortunately, the lumbar puncture was made too late for us to discover any meningeal change.

These 3 cases seem particularly instructive with respect to the pathogenesis of ophthalmoplegic migraine, but one cannot conclude that all cases of ophthalmoplegic migraine are due to a previously established lesion. Only the variation in the nerves involved in the course of successive attacks can refute such a generalization, even though it seems a likely explanation in certain cases.

The ophthalmoplegic migraine seems to be the clinical manifestation of a vasomotor process, accompanied with an exudative reaction of the *seröse Entzündung* type. These vasoexudative reactions located in the area of the posterior cerebral artery, particularly in the pedunculopontobulbar area, affect the pia mater, as well as the nerve tissue. The pain

and the changes in the spinal fluid are explained by the edema produced in the pia mater, and the paralytic symptoms, by a trophic change in the nucleus of the affected cranial nerve. Indeed, without one's denying the participation of the roots of the cranial nerves in the process under consideration, it is impossible to disregard the effective, and probably prevailing, participation of the nuclei, as demonstrated (*a*) in the case in which the lacrimonasal secretion had been suppressed; (*b*) the case in which the paralysis preceded the hemicrania, and (*c*) the cases in which the ophthalmoplegic migraine followed the paralysis of the third cranial nerve, the result of a lesion of the nucleus produced by the action of the poliomyelitis virus.

It remains to consider the condition from which this vascular process arises—a difficult problem. Generally, the cause is impossible to determine. Nevertheless, among the foregoing cases two types of etiologic factors have been encountered, one psychic and the other chemical. The whole process suggests the beginning of various allergic manifestations, generally occurring on a diathesic basis, i. e., on a congenitally predisposed ground, but sometimes also on a ground not predisposed, the diathesis being created under one's own eyes and the living matter retaining, so to speak, the memory of the lived experiences and acquiring the tendency to relive them on the occurrence of various external or internal events.

The treatment of this disorder has not advanced since the time when Charcot recommended bromide and quinine bromide, except that belladonna and phenobarbital have been added.

In accordance with the hypothesis, which I have since given up, of the occurrence of a localized neurologic infection, I used roentgen therapy in a case. Since the good results obtained in this case were encouraging, I was ready to repeat this treatment at the first opportunity. The happy coincidence in which the patient was rapidly cured of the ophthalmoplegic migraine after an unlooked-for febrile episode, without modifying my impression of the favorable therapeutic effect of the radiation on the ophthalmoplegic migraine, diverted my mind from the previous hypothesis (which may be applicable in exceptional cases) to the assumption of a disease due to a vasoexudative crisis, a hypothesis corroborated by the clinical history of the first attack in case 10, and by subsequent observations and predisposed us to a trial of pyretotherapy. Suitable cases soon presented themselves, and the results obtained with the pyretotherapy conformed with my expectations.

Case 14.—A man aged 50, a trade electrician, who had no history of migrainous antecedents, hereditary disease or syphilis and who was free from personal disease, in August 1942, four weeks prior to his admission to the hospital, while at work, had onset of headache, which involved the left side of his head, progressed with excruciating pain and was accompanied with severe nausea. A day after the onset

of the hemicrania the pain became more violent, and ptosis of the left upper eyelid appeared. The patient had diplopia while lifting his eyelid with his hand. These symptoms remained without change. On his admission (September 2) acetylsalicylic acid and other sedatives did not relieve his pain.

Examination revealed ptosis of the left eyelid, with the eyelid turned outward; normal pupillary, deep and cutaneous reflexes and normal sensibility. The blood picture was normal; the Wassermann reaction was negative, and the urea measured 0.26 Gm. per hundred cubic centimeters. The spinal fluid was not under pressure. The protein was 0.33 Gm. per hundred cubic centimeters; the cell count was 1 per cubic millimeter (lymphocytes); the Wassermann reaction was negative, and the reactions to the Nonne-Apelt and Pandy tests were negative.

On September 22, an injection of sulfosine (sulfur in oil) was given, and the temperature rose to 102.2 F. When the temperature returned to normal, the next morning, there was a radical change. After forty days of continuous suffering, the patient became free from pain. The ptosis of the left eyelid was somewhat relieved. The next day, however, the pain recurred in violent form, and the ptosis became accentuated, this state continuing for the next six days. On the seventh day dmelcos was injected, and the temperature rose to 102.2 F. for two days. The ptosis was decreased, and the eyeball could be rotated in all directions. Four days later pain reappeared, being located in the right half of the occiput. We induced a third febrile attack, but the pain did not cease. Five days later we induced another febrile attack. This time the pain disappeared completely, the ptosis was less severe and the eyeball could be rotated in all directions. Five days later we induced another febrile attack, and a week later the patient was discharged, fully recovered.

After that, having been deprived of our department during the German occupation, we were unable to carry on the treatment. We have since applied pyretotherapy in the second attack of ophthalmoplegic migraine in case 10, with satisfactory results, as well as in the next case to be reported.

Case 15.—A woman aged 25 had no history of hereditary disease or of syphilis. She had malaria at the age of 15. On Nov. 10, 1947 she was admitted to the hospital complaining of severe headaches, which involved only the right half of the head. The onset was on Aug. 15, 1947, accompanied with reddening of the right side of the cheek. The duration was for eight days, and after this period the symptoms disappeared, returning to normal except for a feeling of heaviness in the right side of the head. On October 20 the hemicrania reappeared, this time accompanied with nausea and ptosis of the right eyelid.

Examination revealed a blood pressure of 130 systolic and 80 diastolic, ptosis of the right eyelid and paralysis of the internal rectus muscle of the right eye. Nothing else of significance was found on examination.

The blood picture was normal. The Wassermann reaction was negative; the urea measured 0.41 Gm. and the sugar 0.98 Gm., per hundred cubic centimeters. The urine was normal in all aspects. Examination of the spinal fluid revealed 0.33 Gm. of albumin and a cell count of 4 per cubic millimeter (lymphocytes); the Wassermann reaction of the fluid was negative, and the Pandy and Nonne-Apelt tests gave negative reactions for globulin.

On November 19, we induced the first febrile attack, and the temperature rose to 103.8 F., after which the pain became slighter. Three days later a second febrile attack was induced, with the temperature rising to 102.3 F. The ptosis and the paralysis of the internal rectus muscle were improved. The patient could then raise her eyelid, and the headaches were not so severe. Three days later the headaches again became severe and the paralytic phenomena were more complete. Improvement became clearer after the third febrile attack, with the temperature reaching 104.F.(40 C.). This time the pain was less pronounced, and the voluntary move-

ments of the eyelid and the eyeball were obviously increased. We added three febrile attacks, with temperatures of 102.2, 102.5 and 103.6 F., during the period up to December 10. The improvement was progressive after each febrile attack, and the patient was discharged as fully recovered on December 21.

On the basis of these clinical studies, we believe that pyretotherapy when appropriately applied at the onset of ophthalmoplegic migraine can be considered to give excellent therapeutic results. This conclusion is in accordance with the results obtained by Dattner, who applied this treatment to common migraine in 1930, a fact of which I have just been informed.

The effect of this form of therapy seems to be explained by the vasodilation produced by the febrile attack, a change which probably facilitates the resorption of the exudate responsible.

SUMMARY

There is no difference between the clinical features of attacks of ophthalmoplegic migraine with a migrainous basis and those of the condition with a nonmigrainous basis.

The seizures of the ophthalmoplegic type are usually much longer than those of common migraine.

The cranial nerve affected is not always the same in successive seizures. The process can affect other cranial nerves than the oculomotor: It may involve motor (seventh), sensory (fifth or eighth) or vegetative (tenth, lacrimonasal nucleus) nerves.

In some cases there is alteration of the spinal fluid, a change in favor of the hypothesis of the vasoexudative pathogenicity of ophthalmoplegic migraine.

The factors that might initiate this vasoexudative process in the brain stem are multiple: 1. In 3 cases (cases 7, 9 and 10) the cause was psychic. 2. In another case (case 10) it was of chemical nature (sting of a wasp). 3. In 1 case (case 10), the ophthalmoplegic migraine, having had its onset after a chemical injury (sting of a wasp), recurred four years later, but on the other side, after a psychic trauma. That this diversity of factor produced the same organic reaction is interesting, not only with respect to the cause of the ophthalmoplegic migraine, but also from the standpoint of psychosomatic medicine. 4. In 2 other cases (cases 11 and 12) the ophthalmoplegic migraine developed after a lesion of the nucleus of the third cranial nerve, due to the poliomyelitis virus, this lesion having apparently created a "thorn" *(point d' appel)*, which acted as an irritant to produce the subsequent attacks of ophthalmoplegic migraine. 5. In another case (case 13) the condition developed after an acute meningeal reaction due to an unknown agent, this lesion having apparently created another "thorn."

Pyretotherapy, when applied at the onset of the attack, is an efficacious therapeutic method.

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EFFECTS OF INANITION ON THE CENTRAL NERVOUS SYSTEM

An Experimental Study on the Guinea Pig

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THE SUBJECT of inanition in relation to growth and structure was reviewed by Jackson [1] in 1925. Since that time few investigators [2] have concerned themselves with the possible effects of starvation on nerve cells in animals and in man. From the literature it is impossible to formulate a clear picture of the effects produced by starvation. The studies of recent, as well as earlier, writers [3] lack uniformity, and results

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(Footnote continued on next page)

in experimental animals have been inconsistent. A similar criticism applies to other conditions, such as the effects of anoxia, fatigue, electric shock and chemical poisons. Results in some of the earlier studies of inanition are difficult to evaluate because the methods used were inadequately described. Other reports have dealt with only one animal, or with only a few sections of one brain. A few articles have been entirely speculative. To what extent the brain may suffer from severe inanition is unknown at present.

Experimental studies on the guinea pig were undertaken in an attempt to arrive at a solution of this problem by instituting adequate controls and by employing recently improved technical methods of fixation and staining of brain tissues. Attention will be focused on changes in the nerve cell body, especially in the Nissl pattern, following inanition. A limited number of attempts to study changes in behavior and retention of learning in starved animals will also be considered.

MATERIALS AND METHODS

Healthy adult male guinea pigs were used. The first group consisted of 24 animals, whose initial weights varied from 290 to 740 Gm. The second group consisted of 11 guinea pigs, weighing between 465 and 630 Gm. Four other animals, weighing 270 to 360 Gm., served as the controls for the first two groups. The control animals were fed a complete diet fortified with ascorbic acid [4] and were permitted to eat as much as they wanted. All animals, control as well as experimental, were given as much water as they would drink and had access to salt blocks. Each guinea pig that was starved was kept in a separate wire cage. The animals of the first group received no food but had access to unlimited water and salt. Those of the second group were fed biscuits made of a mixture of the complete guinea pig diet and celluflour.® The ingredients of this mixture were 1 part guinea pig diet plus 2 parts flour, or 1 part balanced diet plus 1 part celluflour.® The amount of biscuit fed each animal was equal in weight to the amount of fully balanced diet that a normal guinea pig of similar weight would eat, a quantity determined for about 2 dozen animals preliminary to the present study.

A third group consisted of 12 guinea pigs, weighing 300 to 460 Gm. They were fed the balanced guinea pig diet, water and salt for a period necessary for complete

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training in running a simple alternation maze.[5] After they had learned the running of this maze to the point of perfection, they were divided into two subgroups of 6 animals each. One subgroup served as a control, while the animals of the other subgroup were starved; i. e., they received only water and salt. On the eighth day of inanition the animals were retested in the maze and were subsequently restored to health, when possible, by the feeding of lettuce leaf, orange juice and a paste made of the complete guinea pig diet.[4] After seven days of feeding the recovered animals were retested in the maze (fourteen days after the initial learning was completed). At that time, in order that the number of animals in the inanition series might be enlarged, 4 of the control animals of this group were starved by the withholding of all food. The remaining 2 animals served as controls for this subgroup. The daily weight of the animals was recorded throughout all experiments.

Sixteen of the 24 guinea pigs in the first group died. As quickly as possible thereafter (one to thirteen hours after death) the brains were removed and fixed by immersion in solution of formaldehyde U. S. P. (1:4). All other animals of the first and second groups were killed by a perfusion through the heart of solution of formaldehyde U. S. P. (1:4) made isotonic with sodium chloride and containing acacia.[6] The perfusion pressure was 65 to 70 mm. of mercury. Control animals were similarly perfused after being anesthetized with pentobarbital sodium. Killing of the starved animals was delayed until the last possible moment, at which time they exhibited symptoms of collapse and impending death. The symptoms of collapse were extreme emaciation, loss of righting reflexes, convulsions, dyspnea and apparent loss of sensations.

The brains of all animals were placed in solution of formaldehyde U. S. P. (1:4) after the perfusion had been completed. They were embedded in pyroxylin of low viscosity for serial sectioning at 40 microns. Every tenth section was stained by the buffered thionine technic.[7] Selected sections from the brains of control animals were stained in the same dish with the series of sections from each experimental animal at a p_H of 4.6. Alternate tenth sections from the brains of the experimental and the control animals were stained by a method for myelin sheaths.[8] No other staining technics were employed. However, the thionine method when properly used is adequate for demonstrating some features of all glial elements.

RESULTS

The table summarizes data concerning the loss of weight and duration of experiments for the starved animals used for histologic study. The 4 control animals for groups 1 and 2 were killed eleven days after the beginning of the experiments. Their gains in weight were 60, 90, 90 and 95 Gm., respectively. Two other controls for group 3 gained 55 and 75 Gm., respectively, in the same period.

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Loss of Body Weight and Duration of Starvation in Experimental Animals

Animal Number	Body Weight		Loss of Weight		Duration of Starvation, Days	Portion of Normal Diet *
	Initial	Final	Gm.	Percentage		
Animals of First Group						
401	390	245	145	37	10†	..
403	370	220	150	40	8†	..
405	360	200	160	44	11†	..
406	370	215	155	42	10†	..
410	300	160	140	46	8†	..
414	420	230	190	45	9†	..
415	490	295	195	40	9†	..
416	440	250	190	43	9†	..
421	430	230	200	42	8†	..
423	430	260	170	40	8†	..
426	500	290	210	42	15†	..
427	500	270	230	46	11†	..
428	500	290	210	42	12†	..
429	400	275	185	40	9†	..
431	680	485	195	28	7†	..
433	740	490	250	33	10†	..
402	375	220	155	41	11	..
404	390	220	170	43	10	..
409	290	155	135	46	9	..
411	310	185	125	40	9	..
420	410	210	200	48	10	..
425	490	270	220	45	13	..
430	480	260	220	45	16	..
432	650	400	250	39	10	..
Animals of Second Group						
7	465	385	80	17	25	½
9	483	332	179	37	40	½
12	497	287	210	42	27	½
1	595	357	238	40	19	⅓
13	532	430	102	19	29	⅓
18	630	473	157	25	14	⅓
19	588	470	118	20	15	⅓
112	544	277	267	49	27	⅓
117	505	375	130	23	15	⅓
118	527	350	177	33	16	⅓
123	628	410	218	34	24	⅓
Animals of Third Group						
400	330	220	110	33	10†	..
401	300	190	110	37	7†	..
402	340	210	130	38	8†	..
403	400	220	180	45	10†	..
464	400	260‡	140	35	8	..
465	400	260‡	140	35	8	..
467	430	270‡	160	37	8	..
468	460	270‡	190	41	8	..
469	440	275‡	165	38	8	..
470	400	230‡	170	43	9	..

* All animals in the first and third groups received no food.

† The animal died. The brains of animals in group 1 were removed and placed in dilute solution of formaldehyde U. S. P. (1:4).

‡ Weight on the day feeding was resumed.

The 16 animals that died from inanition before they could be killed by the perfusion-fixation technic, and whose brains were fixed by immersion in solution of formaldehyde U. S. P. (1:4), showed neuronal changes not unlike many of those that have been described by previous investigators. Sections of the brain prepared by the method for myelin sheaths stained lighter than similar sections from the animals that had been killed by perfusion and lighter than sections from the control animals. Similarly, the sections stained by the technic for Nissl substance appeared lighter. Microscopic examination demonstrated marked generalized changes in all parts of the brain. Some nerve cells were considerably shrunken; others were swollen. The Nissl body patterns were clouded, and in some instances there appeared to be almost complete chromatolysis. Many nerve cells were vacuolated. The perineuronal and perivascular spaces were much larger than those in sections from the control animals. Even in the specimens that were fixed by immersion within one hour after death, such changes were widespread. The similarity between this picture and that obtained in human brain material removed at autopsy and fixed by immersion in solution of formaldehyde U. S. P. was striking. This is in accord with other recent observations on postmortem changes.[9]

The sections from the brains of the 8 animals of the group that had received no food and that had been killed by perfusion of the vascular system were indistinguishable at low magnification from similar sections of the control animals in respect to the intensity of staining and brilliancy of the color. Microscopic examination of the sections stained by the myelin sheath technic showed no difference between the brains of the starved animals and those of the controls. The microscopic appearance of the thionine-stained sections of most of the 8 animals was similar to that of comparable sections of brains from the control animals, but detailed examination with higher magnification revealed a few cytologic differences. The most clearly perceptible difference was in the large nerve cells of the brain stem, principally those of the cranial nerve nuclei, the red nucleus, the cochlear and vestibular nuclei, the pontile nuclei and the reticular formation, as well as in the nuclei of the cerebellum. The Nissl body patterns of these cells were unlike those of similar cells in the control animals in respect to distribution of the basophilic material. Some of the cells showed a clear peripheral zone of cytoplasm with a gradually increasing density of Nissl substance toward the nucleus (fig. 1).

A change was observed also in some of the medium-sized and small cells of the brain stem in the sections from the 8 animals that had been

9. Koenig, R.: Post-Mortem Changes Within the Central Nervous System, Anat. Rec. **103** (March) 1949.

killed by perfusion with solution of formaldehyde U. S. P. (1:4). A variable amount of irregularly arranged clear peripheral cytoplasm could be seen in these cells. This was due not to vacuolation or accumulation of fluid at the cell periphery, but to an arrangement of the fine particles of Nissl substance in a pattern that may be described as "scalloping." Often this arrangement of Nissl substance was encountered not around the entire circumference of a nerve cell but only on one side.

The thionine-stained sections of the brains of control animals contained cells that showed decrease in size of Nissl bodies toward the periphery and occasional clear areas near the periphery. Some small cells had the "scalloping" of fine Nissl substance, like that just described. However, the number of cells showing these phenomena in any control

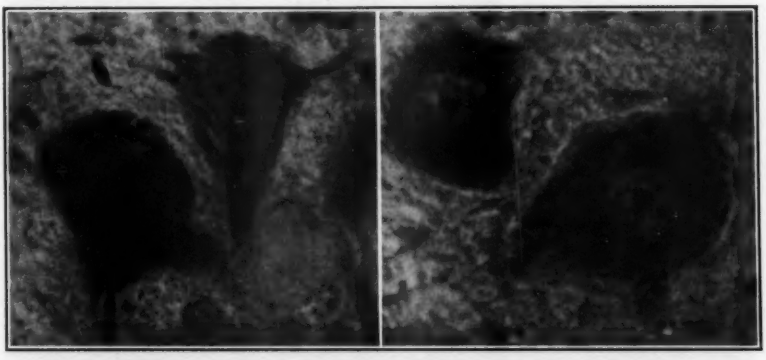

Fig. 1.—Left, large nerve cells in the red nucleus of a control animal; right, large nerve cells in the red nucleus of animal 406, starved for ten days and killed when it had lost 42 per cent of the body weight. Thionine stain; × 815.

brain was considerably less than that in any one of the animals of the inanition series.

The sections of the brain of animals that had lived on a diet one-half or one-third the normal amount for fifteen to forty days before being killed by perfusion with the fixing fluid showed no significant changes when examined with low magnification. With higher magnification, detailed examination of the nerve cells of sections stained with the buffered thionine method revealed the same picture as that encountered in the animals of the first group, i. e., those that had received no food. More of the large cells in these sections showed a peripheral clear zone of cytoplasm than in the controls; more of the small cells showed the peripheral "scalloping" of fine particles of Nissl substance. Otherwise, most sections were indistinguishable from those of the brains of the control animals. If there was any difference between the sections in

the first and those in the second group of experimental animals, it was manifested in a slightly greater number of affected cells in the second group. There appeared to be no correlation between the severity of such alteration and the percentage of loss of body weight during the experiment.

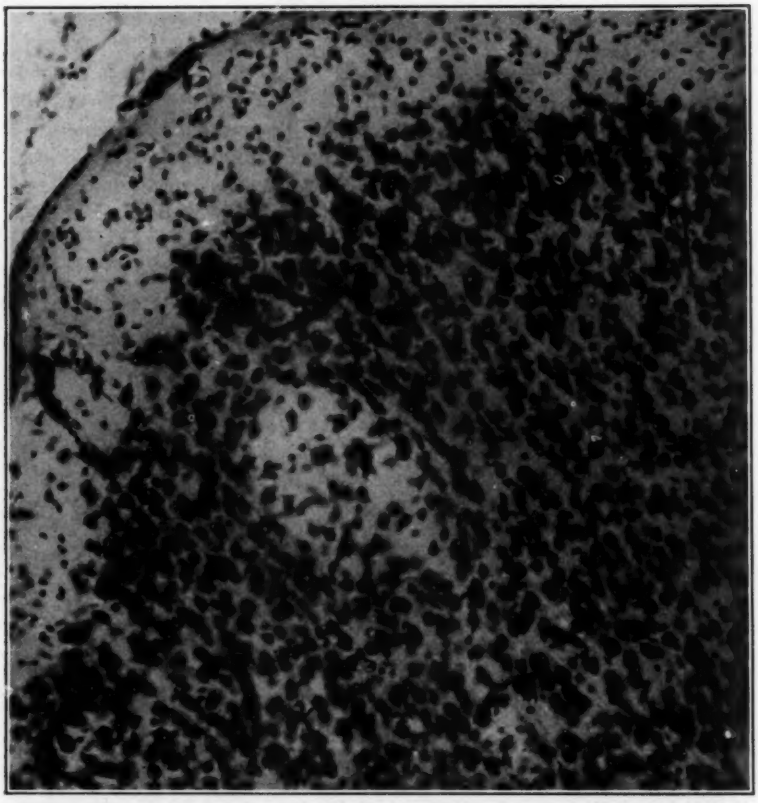

Fig. 2.—Pale area in the cerebral cortex of animal 12, which lost 42 per cent of the body weight after twenty-seven days on a diet one half the normal in amount. Thionine stain; × 190.

In only 1 of the experimental animals that have been killed by the perfusion-fixation method were there noted changes other than those already described. The sections of the brain of that animal (guinea pig 12) contained a few small, apparently perivascular, pale areas scattered throughout the cerebral cortex (fig. 2). Within these areas were a few nerve cells with vacuolated cytoplasm.

On the whole, the differences between the control animals and the animals that had suffered complete starvation or had lived on limited diets for various periods were surprisingly few and unimpressive; not only were the nerve cell bodies and nerve fibers quite intact; the astrocytes and other glial cells, too, appeared to be unaffected and were no more or less numerous than in the controls.

The animals of the third group were not studied from the standpoint of possible cytologic changes but were given the learning tests. The behavior of these, as well as all other, animals during the progress of starvation was studied at frequent intervals each day. The activity of the guinea pigs increased greatly during the early part of the period of fasting. They made calling sounds when there were noises in or near the animal room. After the first three to seven days their activity diminished, until they moved very little of their own volition. Finally, they were often found nearly comatose, with their forelimbs against the edge of the water bowl or with their heads against the corner of the cage or lying on their sides on the floor of the cage. An attempt was made to revive them just before they reached the stage of collapse by forcing them to begin to eat and drink.

All the animals of group 3 were first trained to the point of perfection on the alternation maze. One or two weeks thereafter they were retested to make sure that they had retained memory of the maze situation. The period of fasting was started only after it had been demonstrated that learning was complete. An attempt was made to retest the starved animals after the effects of inanition had become clearly manifested. This was unsuccessful, except in 1 instance, because of weakness. In the 1 successful attempt, the guinea pig ran ten consecutive errorless trials, comparable to the results for the unstarved controls. Four of the animals died before they could be restored to health after inanition, and 6 were successfully refed to the point of good health. Retesting of these 6 animals in the maze situation revealed no significant changes in retention of the learned problem.

COMMENT

Changes in brain structure in man and animals have been attributed to the effects of inanition by a number of previous investigators. It seems clear from the present study that such changes as may have been due to inanition have been confused with those that resulted from inadequate fixation by immersion and from postmortem autolysis. Recent studies in this laboratory by Koenig [9] have demonstrated that postmortem artefacts appear in the brain as early as one-half hour after death in normal guinea pigs. Some authors [2a] have described additional changes in the nature of alterations in blood vessels and have suggested

the possibility that vitamin deficiency plays a role in such changes. A few workers[10] have described the pathologic changes involving the neuroglia after periods of inanition. The present study on guinea pigs revealed only 1 instance of possible vascular alteration and no difference between the neuroglia in the controls and that in the animals that had been starved.

Whether the slight alterations observed in the nerve cells of the brain stem in the present experiments were actually due to nutritional deficiency affecting the metabolism of the neurons directly or whether they were secondary to accumulation of the products of catabolism and histotoxic anoxia we cannot say. It is entirely possible that they may have been due to uncontrollable initial enzymatic autolysis in the cells of dying animals and were not, strictly speaking, the result of the inanition per se. On the other hand, it would seem possible that there was some call on the proteins of the nerve cell cytoplasm after inanition had gone beyond the stage at which the more readily available carbohydrates, fat and proteins had become exhausted. In the animals of group 2, maintained for somewhat longer periods than those of group 1 by being fed quantitatively limited diets, the greater possibility of avitaminosis, autointoxication and altered metabolism should be considered. It was noted that the cytologic changes in question were slightly more pronounced in some of these animals than in the animals of group 1 that had received no food during shorter periods.

The attempt to observe alteration in retention of a learned problem revealed little of significance. Certainly, under the conditions of the experiments reported here there was no evidence of impaired memory resulting from the periods of inanition.

SUMMARY

Healthy young adult male guinea pigs were subjected to inanition either by withholding all food or by feeding them a diet quantitatively reduced by one half or two thirds. They lost 17 to 49 per cent of the body weight. The brains were studied histologically and were compared with similarly prepared brains of animals fed a complete laboratory diet. Only in the animals that died during the final stages on inanition and whose brains were fixed in solution of formaldehyde U. S. P. by immersion after death were marked diffuse neuronal changes observed. These consisted in lighter staining of all elements of the brain, chromatolysis, shrinkage or swelling, vacuolation of the cytoplasm and enlarged perineuronal spaces. These changes were in the nature of artefacts due to postmortem change and delayed fixation and apparently were not due to inanition.

10. Andrew, footnotes 2a and c. Garofeanu and Ornstein.[21]

The brains of animals that were killed by perfusion fixation while in a state of collapse just preceding death from inanition were very little different from those of control animals that were killed by perfusion fixation after anesthetization with pentobarbital sodium. Some of the large nerve cells of the brain stem had reduced amounts of Nissl substance in the cytoplasm, often manifested by a wide clear zone at the cell periphery. Some of the medium-sized and small nerve cells exhibited a similar phenomenon in which the Nissl body pattern assumed a "scalloped" appearance peripherally. Even in the sections from the control animals, a few large and small nerve cells could be seen with a somewhat similar distribution of Nissl substance in the cytoplasm, but the phenomenon was much more frequently encountered in the animals that had been starved for various periods. No alterations in the neuroglia were encountered in any of the experiments, and in only 1 animal were small, pale areas containing vacuolated neurons observed.

In other experiments, an attempt was made to determine impairment of memory of a learned problem in guinea pigs subjected to inanition. No significant alterations in retention of learning were observed.

THE VOMITING CENTER

A Critical Experimental Analysis *

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VOMITING, or emesis, is perhaps the reflex response which makes most widespread use of the motor systems of the animal organism. Involved in this complex pattern of activity are salivation; spasmodic respiratory movement, effected by the antagonistic action of the inspiratory and expiratory musculature; gastrointestinal reactions of a specialized nature, and postural characteristics of the head, body and appendages typically adapted to the process of expulsion of the gastric contents. In addition, there are psychic and cardiovascular effects which fit into the total integrated response.

Although the movements of the different muscle groups used in vomiting were not understood until the publication of the classic work of Cannon,[2] the orderly sequence of events during emesis had already led Giannuzzi,[3] in 1865, to postulate the existence of a "vomiting center."

In the past few decades it has been the vogue for physiologists to label as a center any part of the brain which yielded a given response when stimulated by any of a variety of means. It was generally believed that a center is an aggregate of cells the sole function of which is the automatic power of producing a specialized integrated response. Modern physiology of the central nervous system makes the idea of isolated groups of cells as centers for separate and distinct functions no longer tenable. At present a "center" is conceived as a group of neurons interconnected in many ways and concerned with the execution of a certain coordinated response. But no center has as its sole function the

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* A preliminary report of this work appeared in *Federation Proceedings* (8:13, 1949).

1. Footnote deleted.

2. Cannon, W. B.: The Movements of the Stomach Studied by Means of the Roentgen Rays, Am. J. Physiol. 1:359-382, 1898.

3. Giannuzzi, G.: Ueber die Wirkung des Tartarus stibiatus, Centralbl. f. d. med. Wissensch. 3:129-131, 1865.

complete regulation of any single activity; rather, the neurons under consideration, among their diverse functions, can act cohesively and be instrumental in coordinating a given response.

It follows from this concept that stimulation of the central neuron complex in favorable circumstances should result in the expression of the given regulated response and, second, that destruction of the region in question should either totally eliminate the response or cause the integrated chain of events to be dissociated; i. e., isolated parts of the pattern may still be separately elicitable. Thus, any evidence presented for the existence of a center should satisfy both the aforementioned conditions.

We have attempted in this experimental analysis to ascertain the precise location of the vomiting center by utilizing methods which would fulfil the requirements of these two basic criteria.

STIMULATION EXPERIMENTS

Previous investigators [4] have had no success in obtaining emesis by electrical stimulation of the medulla oblongata. Miller and Sherrington [4a] were able to evoke vomiting reflexly with noxious fluids but failed to do so by faradizing the floor of the fourth ventricle. Laughton [4b] stimulated the dorsal nucleus of the vagus nerve,[5] signified by Hatcher and Weiss as the site of the vomiting center, but elicited no vomiting.

Since 1936, one of us (S. C. W.) has stimulated the lower portion of the brain stem to obtain various autonomic responses in more than 200 animals (cats, dogs and monkeys) but has never observed any response which could be called vomiting. Nevertheless, a suggestive reaction obtained on stimulation of the medulla was an unusual augmented respiratory movement.[6] A complete survey of this spasmodic respiratory act, which may take any one of several forms, i. e., retching, sneezing or coughing, was reported from this laboratory in 1948.[7] Most of the experiments were carried out with the use of pentobarbital sodium as the anesthetic, and under this condition vomiting never occurred. It is well known that barbiturates in general make the vomiting center refractory to emetic stimuli.

4. (*a*) Miller, F. R., and Sherrington, C. S.: Some Observations on the Bucco-Pharyngeal Stage of Reflex Deglutition in the Cat, Quart. J. Exper. Physiol. **9**:147-186, 1915. (*b*) Laughton, N. B.: The Effect on the Stomach of the Stimulation of the Dorsal Vagus Nuclei, Am. J. Physiol. **89**:18-23, 1929. (*c*) Walton, F. E.; Moore, R. M., and Graham, E. A.: The Nerve Pathways in the Vomiting of Peritonitis, Arch. Surg. **22**:829-837 (May) 1931.

5. Hatcher, R. A., and Weiss, S.: Studies on Vomiting, J. Pharmacol. & Exper. Therap. **22**:139-193, 1923.

6. Wang, S. C., and Ranson, S. W.: Autonomic Responses to Electrical Stimulation of the Lower Brain Stem, J. Comp. Neurol. **71**:437-455, 1939.

7. Borison, H. L.: Electrical Stimulation of the Neural Mechanism Regulating Spasmodic Respiratory Acts in the Cat, Am. J. Physiol. **154**:55-62, 1948.

In an attempt to avoid anesthesia, we found that the decerebrate cat showed no change in emetic response to lobeline sulfate. The decerebrate cat thus became the preparation of choice for the elicitation of emesis by electrical stimulation of the medulla. Altogether, 20 cats were used for medullary exploration with the Horsley-Clarke stereotaxic instrument. Complete experimental details were recently published elsewhere,[8] but, for the sake of continuity, the results may be summarized here (fig. 1): 1. The region most responsive to electrical stimulation corresponds by histologic verification to the tractus solitarius and its nucleus and a small area on the dorsolateral border of the reticular formation. 2. Thresholds of stimulating current for the vomiting response are such that the minimal intensity is about 8 volts and the frequency threshold in the neighborhood of 50 impulses per second. 3. The response is not abolished after bilateral vagotomy, but the latent period is prolonged. A fact worthy of stress is that stimulation of the areas designated as the vomiting center by Thumas [9] or by Hatcher and Weiss [5] yielded no

Fig. 1.—Diagramatic representation of positive results obtained on stimulation of the medulla. Sections represent levels about 1.5 mm. apart. Circles represent reactive points for vomiting responses. In this figure, and in figures 2, 3 and 4, *DVes* indicates descending vestibular nucleus and tract; *R*, restiform body; *s*, tractus solitarius and its nucleus; *am*, nucleus ambiguus; *SO*, superior olive; *IO*, inferior olive; *CS*, corticospinal tract; *LCN*, lateral cuneate nucleus. From Borison and Wang.[8]

vomiting response. This, however, does not exclude these structures as integral parts of the emetic reflex. Furthermore, this type of acute experiment involving electrical stimulation of the central nervous system does not as a rule furnish evidence for the differentiation of the component parts of the reflex arc. Nevertheless, since no region of the brain stem other than the dorsolateral portion of the reticular formation of the medulla yielded vomiting by stimulation, we may conclude that the coordinating mechanism for emesis is included in the responsive region delimited in this series of experiments (fig. 1).

8. Borison, H. L., and Wang, S. C.: Functional Localization of Central Coordinating Mechanism for Emesis in Cat, J. Neurophysiol. **12**:305-313, 1949.

9. Thumas, L. I.: Ueber das Brechcentrum und über die Wirkung einiger pharmakologischer Mittel auf dasselbe, Virchows Arch. f. path. Anat. **123**:44-69, 1891.

ABLATION EXPERIMENTS

Thumas [9] was able to eliminate the vomiting response to apomorphine, in the dog, by destroying a small midline area in the posterior portion of the rhomboid fossa. Hatcher and Weiss [5] repeated the experiments of Thumas and found that in such animals vomiting could still be elicited reflexly with mercury bichloride. They claimed further that destruction of the ala cinerea results in total disappearance of the emetic response to reflex, as well as to central, emetic drugs. The single experimental protocol presented by Hatcher and Weiss [5] to support this contention showed that the cat, after destruction of the ala cinerea, did not vomit on the oral administration of mercury bichloride but died a short thirty minutes afterward. It is unfortunate that these investigators had chosen to use the acute animal preparation, for the interpretation of negative results in such experiments is always open to question. Furthermore, operations involving destruction of brain tissue notoriously cause swelling and functional impairment of structures in the immediate vicinity of the lesion. It is therefore extremely difficult to determine the exact limits of influence in acute ablation experiments. Indeed, in another communication from Hatcher's laboratory, Koppanyi [10] reported an apparent contradiction to the earlier work of Hatcher and Weiss. He found in 2 dogs with chronic lesions in the dorsal nucleus of the vagus that emesis was still elicitable by oral administration of copper sulfate and that the responsiveness to apomorphine followed an irregular course, ending in an elevated threshold.

Owing to this difference of results following ablation of the ala cinerea, and also to the lack of agreement on the location of the vomiting center itself, we prepared two separate series of chronic animals with lesions in the medulla oblongata. In the one series, the superficial area in the fourth ventricle designated as the vomiting center by Hatcher and Weiss [5] was destroyed; but great care was exercised to make the lesion less diffuse than had been shown by these investigators, so as to limit the ablation to the dorsal vagal nuclei. In the second series, lesions were more deeply placed in the dorsolateral portion of the reticular formation, which yielded emesis on electrical stimulation.

It was realized at the very beginning that, because of the many vital functions involved in this general region, it would be difficult to keep animals alive with deep bilateral medullary lesions. The calculated chances for total elimination of the vomiting response to all emetic drugs in the chronic animals were not very good. It was therefore imperative to determine carefully normal thresholds of emetic drugs for later comparison with dosage required after operation to elicit emesis, if at all elicitable.

10. Koppanyi, T.: Studies in Defecation, with Special Reference to a Medullary Defecation Center, J. Lab. & Clin. Med. **16**:225-238, 1930.

Since the cat was used in the stimulation experiments, it would seem best to use the same species in the ablation series. This presents certain disadvantages, for the cat is rather resistant to the powerful central emetic apomorphine. Indeed, Sollmann [11] stated that the cat requires about fifty times as much apomorphine per unit of body weight as the dog. Even with large doses, the response of the cat to apomorphine is far from consistent. For this reason, the present series of ablation experiments was performed on dogs.

For testing the emetic response in the dog we used apomorphine hydrochloride as a central emetic and copper sulfate as a reflex emetic.

Threshold for Apomorphine.—Dogs weighing from 6 to 10 Kg. were preferred for this study. The animal was first fed, and then 0.1 mg. of apomorphine hydrochloride, freshly dissolved in 1 cc. of distilled water, was injected into the saphenous vein of the unanesthetized dog. The latency of emesis varied from one to five minutes, the average being approximately two minutes. The prompt response to such a small quantity of the substance was striking; also of interest were the absence of side effects and the rapid recovery from nausea which was manifested by the renewed desire to eat appearing only a few minutes after emesis. If vomiting was obtained with 0.1 mg., one-half the dose (0.05 mg.) was tried. If, on the other hand, emesis did not occur with 0.1 mg., twice this dose (0.2 mg.) was given under similar conditions. It is important that no more than a single test was ever made in one day on any particular dog. Of 59 dogs tested, 39, or 81 per cent, responded to 0.1 mg. of apomorphine hydrochloride. Of these, only 9 dogs, or 15 per cent of the total number, vomited when given 0.05 mg. We may thus conclude that 0.1 mg. of apomorphine hydrochloride is the most probable threshold dose for vomiting in a random group of dogs when the drug is given intravenously soon after feeding. For any given dog, the latency of response was remarkably constant and did not vary appreciably with moderate changes in the dose injected. With repeated injections of large or small doses of apomorphine, up to fifteen times in the same animal at short intervals (two to three days), we demonstrated the well known fact that dogs do not develop tolerance to this drug, as to either dosage or latency.

Threshold of Copper Sulfate.—Copper sulfate [12] in 50 cc. of distilled water was administered to the fasted dog via the stomach tube. It is essential for consistent results to deliver the solution of copper sulfate into the empty stomach. A dog which had been fed prior to testing may not vomit with several times the threshold dose. For this reason, food was withheld eighteen hours or more before each test. Altogether, 32 dogs were tested with copper sulfate. Of these, 28 dogs, or 84 per cent, yielded a positive response with 40 mg.; only 7 dogs, or 22 per cent of the total, responded to 20 mg. No dog failed to vomit with 80 mg.[13] We may conclude, therefore, that 40 mg. of copper sulfate is the most probable

11. Sollmann, T.: A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology, ed. 6, Philadelphia, W. B. Saunders Company, 1943, p. 574.

12. Copper sulfate was used in the blue crystalline form, $CuSO_4 \cdot 5H_2O$; all amounts were calculated without including the weight of water.

13. A single apparent exception is to be noted in dog 59 (protocol, page 934). The elevated copper sulfate threshold in this dog is undoubtedly due to the fact that the stomach was not empty at the time the test was made.

threshold dose in a random group of dogs when given under the conditions specified. The emetic response is consistently reproducible, and no animal failed to vomit after any given dose if it had previously vomited with a smaller dose. The latent period of emesis after administration of copper sulfate is longer than that after apomorphine, and the latency is much more variable in different dogs, ranging from five to thirty minutes; these results are to be expected from the reflex nature of the response to copper sulfate.

Operative Procedure.—Pentobarbital sodium (35 mg. per kilogram of body weight) was used for anesthesia. A midline incision was made from the occiput to the cervical portion of the spine, and the nuchal muscles were widely retracted to expose the foramen magnum. The opening was enlarged rostrally to expose the vermis of the cerebellum and the floor of the fourth ventricle. Lesions in the medulla were made with the use of the cold cautery instrument. For superficial lesions, in the ala cinerea, a needle electrode was employed. Deep lesions were made with a bent insulated wire electrode which ended in a small bare loop. This was inserted through the floor of the ventricle, after which the current was turned on and the electrode moved caudalward; the current was turned off before the electrode was removed from the brain. It was hoped that by such means an elongated lesion would be made in the lateral recticular formation with relatively little damage to the surface of the medulla. This objective, however, was not achieved satisfactorily, since leakage of current through the insulation of the electrode caused considerable damage at the surface.

Postoperative Course.—Dogs with superficial lesions in the ala cinerea required little special postoperative care. On the other hand, many of the animals with deep lesions succumbed within twenty-four hours, all showing severe respiratory difficulty before death. The chances for survival were only slightly better when the ablation was carried out in two stages. Most of the dogs which survived the bilateral placement of the deep lesion had trouble related to swallowing. Two were asphyxiated with food in the larynx; many showed pulmonary infection, probably the result of aspiration. For this reason, all animals were maintained on antibiotic therapy [14] during convalescence.

Superficial Lesion and Emesis.—Lesions of various extents in the region of the ala cinerea were successfully produced in 8 dogs. The effect of this procedure on the emetic response is adequately illustrated by the accompanying 4 protocols, in which are outlined the progressive responses to apomorphine and/or copper sulfate. None of the dogs died as a result of the operation, but all but 1 dog (dog 130) were killed for the purpose of histologic study.[15]

Dog 187.—Female; weight 6 Kg. (fig. 2*A*).

Preoperative Tests

Apomorphine hydrochloride: Vomited to 0.05 mg., latency 2 min.

Copper sulfate: Did not vomit to 20 mg.; vomited to 40 mg., latency 14 min.

14. Lederle Laboratories, E. R. Squibb & Sons and Merck & Co. provided us with generous supplies of penicillin preparations.

15. The brains were perfused with solution of formaldehyde U. S. P. (1:10) and embedded in pyroxylin. The location and size of the lesions were mapped out by histologic examination of serial sections.

Postoperative Tests

Apomorphine hydrochloride:

Day 7: Vomited to 0.2 mg., latency 7 min.

Day 32: Vomited to 0.2 mg., latency 2.5 min.

Day 40: Did not vomit to 0.1 mg.

Copper sulfate:

Day 46: Did not vomit to 40 mg.

Day 54: Vomited to 80 mg., latency 16 min.

Dog killed on sixtieth postoperative day.

Comment: This dog showed only a slight increase in both the apomorphine and the copper sulfate threshold as a result of the operation. The lesion, although correctly placed, was not as extensive as desired.

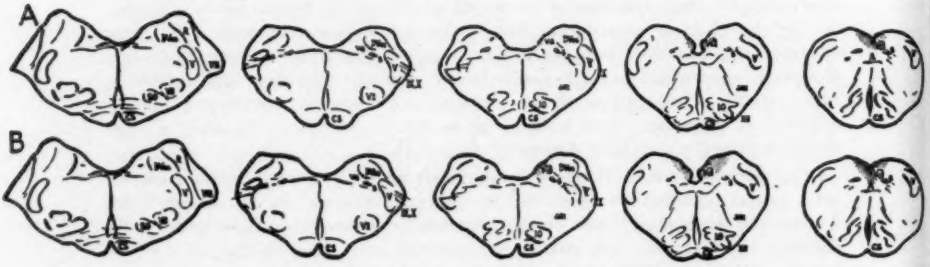

Fig. 2.—*A*, serial sections of the medulla of dog 187; *B*, serial sections of the medulla of dog 99. Lesions are represented by dotted areas; *va* signifies dorsal sensory nucleus of the vagus.

Dog 99.—Female; weight 5.4 Kg. (fig. 2*B*).

Preoperative tests

Apomorphine hydrochloride: Vomited to 0.1 mg., latency 3 min.

Postoperative tests

Apomorphine hydrochloride:

Day 3: Did not vomit to 0.5 mg.

Day 9: Did not vomit to 1.5 mg.

Dog killed on ninth postoperative day.

Comment: This dog was one of the first with a superficial lesion. While the area of ablation was only slightly larger than that of dog 187, the threshold for apomorphine was increased at least fifteenfold over the preoperative level. No tests with copper sulfate were made.

Dog 59.—Male; weight 10.0 Kg. (fig. 3*A*).

Preoperative tests

Apomorphine hydrochloride: Did not vomit to 0.1 mg.; vomited to 0.2 mg., latency 1.2 min.

Copper sulfate: Did not vomit to 160 mg.; vomited to 240 mg., latency 25 min.

Postoperative tests

Apomorphine hydrochloride:

Days 14, 21: Did not vomit to 1.0 mg.

Days 28, 31: Did not vomit to 2.0 mg.

Copper sulfate:

Day 24: Vomited to 320 mg., latency 14 min.

Day 30: Vomited to 320 mg., latency 25 min.

Day 32: Did not vomit to 240 mg.

Dog killed on thirty-second postoperative day.

Comment: The lesion was moderately extensive, encroaching on the tractus solitarius, especially on the right side. This animal, used at the beginning of the experimental series, was not fasted prior to the test with copper sulfate, either before or after operation; consequently, he responded only to large doses. The emetic threshold to copper sulfate

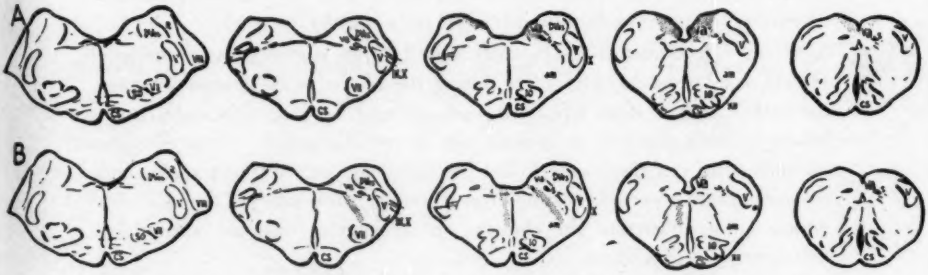

Fig. 3.—*A*, serial sections of the medulla of dog 59; *B*, serial sections of the medulla of dog 53. Lesions are represented by dotted areas.

appeared to be increased only slightly. The threshold to apomorphine was increased at least ten times.

Dog 130.—Female; weight 8.3 Kg.

Preoperative tests

Apomorphine hydrochloride: Did not vomit to 0.1 mg.; vomited to 0.2 mg., latency to 1.5 min.

Copper sulfate: Did not vomit to 40 mg.; vomited to 80 mg., latency 15 min.

Postoperative tests

Apomorphine hydrochloride:

Days 3, 8, 24: Did not vomit to 1.5 mg.

Day 45: Did not vomit to 2.0 mg.

Day 95: Did not vomit to 10 mg.[16]

16. Lower thoracic and lumbar sympathectomy was performed twenty-four days prior to this test, for another purpose; however, sympathectomy was shown to have no effect on the threshold to apomorphine (unpublished data).

Copper sulfate:

Day 6: Did not vomit, but retched weakly to 80 mg.
Day 32: Vomited to 80 mg., latency 25 min.
Day 48: Did not vomit to 80 mg.
Day 65: Vomited to 160 mg., latency 37 min.
Day 73: Vomited to 480 mg., latency 13 min.

Comment: This dog is alive at the time of this report, but the lesion, so far as could be judged during operation, is approximately equivalent to that of dog 59. The threshold to apomorphine is increased over the control values at least fiftyfold, but the change in threshold to copper sulfate is insignificant.

The result on the emetic response of superficial ablation in the medulla oblongata leads to the following conclusion: Bilateral lesions in the region of the dorsal nucleus of the vagus make the animal permanently refractory to large doses of apomorphine, whereas the threshold of emesis to copper sulfate is increased only slightly, if at all.

Deep Lesion and Emesis.—Although 11 dogs survived the immediate effects of bilateral medullary ablation in the region of the lateral reticular formation, only 5 dogs lived long enough and were in sufficiently good health to make possible valid tests with the emetic drugs. None of these animals died, but they were killed for histologic examination at the end of postoperative periods lasting from three to ten weeks. The protocols which follow illustrate the changes in the emetic response caused by this operative procedure.

Dog 53.—Female; weight 6.4 Kg. (fig. 3*B*).

Preoperative tests

Apomorphine hydrochloride: Did not vomit to 0.1 mg.; vomited to 0.2 mg., latency 2 min.

Postoperative tests

Apomorphine hydrochloride:

Day 6: Vomited to 0.2 mg., latency 10 min.

Copper sulfate:

Day 13: Vomited to 80 mg., latency 13 min.

Dog killed on twenty-first postoperative day.

Comment: This is the first dog in which the placing of a bilateral deep lesion was attempted. No change in the threshold to apomorphine resulted. Although no control test with copper sulfate was made, it can be assumed, since a small dose elicited vomiting after operation, that the threshold to copper sulfate was not significantly changed. Lesions were found to be not only asymmetric but also not properly placed.

Dog 12.—Female; weight 7.1 Kg. (fig. 4*A*).

Preoperative tests

Apomorphine hydrochloride: Vomited to 0.1 mg., latency 2 min.

Copper sulfate: Vomited to 40 mg., latency 14 min.

Postoperative tests

Apomorphine hydrochloride:

Days 22, 29, 38: Did not vomit to 1.0 mg.

Day 62: Did not vomit to 2.0 mg.

Day 66: Did not vomit to 5.0 mg.

Copper sulfate:

Days 10, 40, 45, 60, 68: Did not vomit to 160 mg.

Day 36: Vomited ineffectively to 240 mg., latency 20 min.

Day 54: Vomited ineffectively to 240 mg., latency 20 min.

Dog killed on sixty-eighth postoperative day.

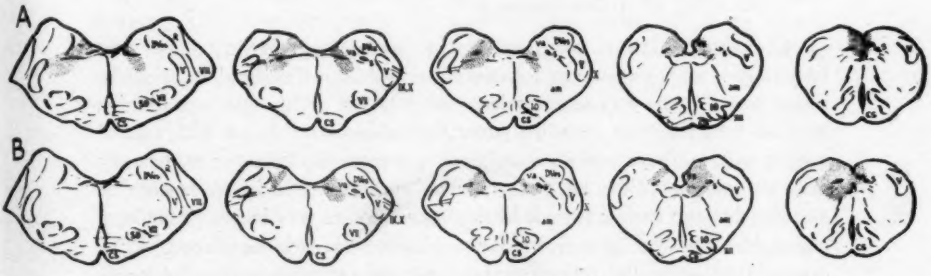

Fig. 4.—*A*, serial sections of the medulla of dog 12; *B*, serial sections of the medulla of dog 183. Lesions are represented by dotted areas.

Comment: In this dog a small corneal ulcer developed on the left eye as a result of the absence of the corneal reflex on that side; there were mild left nystagmus and deviation of the tongue to the right. The buccal phase of deglutition was lost, so that the dog had to be fed manually. All these signs, except for the deviation of the tongue, eventually disappeared. The body weight showed a steady increase to 8.3 Kg. at the time the animal was killed. The threshold to apomorphine was increased at least fiftyfold by the operation, and that to copper sulfate about sixfold. With 240 mg. of copper sulfate, the animal vomited a scant amount of mucus without opening its mouth. The lesions were symmetrically placed, but the one on the left side produced much more damage to the dorsolateral portion of the lateral reticular formation than that on the right.

Dog 183.—Female; weight 6.7 Kg. (fig. 4*B*).

Preoperative tests

Apomorphine hydrochloride: Vomited to 0.05 mg., latency 1.5 min.

Copper sulfate: Did not vomit to 20 mg., vomited to 40 mg., latency 8 min.

Postoperative tests

Apomorphine hydrochloride:

Day 10: Vomited to 1.0 mg., latency 3.5 min.

Days 22, 31: Did not vomit to 1.0 mg.

Day 38: Did not vomit to 2.0 mg.

Copper sulfate:

Day 7: Vomited to 160 mg., latency 13 min.

Days 36, 44: Did not vomit to 160 mg.

Days 45, 48: Did not vomit to 320 mg.

Day 52: Vomited ineffectively to 320 mg., latency 21 min.

Day 58: Vomited ineffectively to 320 mg., latency 12 min.

Dog killed on sixtieth postoperative day.

Comment: The bilateral lesions in this animal were carried out in two stages, with an interval of twelve days. The threshold to apomorphine was thereby increased at least forty times. Although some bluish mucoid material was expelled after the administration of 320 mg. of copper sulfate, there was no coordination in movements of the respiratory muscles and mandible characteristic of vomiting. It is reasonable to assume that the emetic threshold to copper sulfate was increased at least eightfold. On the fifty-ninth day a bloody diarrhea developed. The dog was killed on the following day, and autopsy revealed hemorrhagic patches in the gastrointestinal tract, undoubtedly due to copper sulfate poisoning.

From the protocols on experiments involving deep medullary lesions, the following conclusion is reached: If the bilateral lesion in the floor of the fourth ventricle is extended to include the dorsolateral border of the lateral reticular formation, the animal not only becomes refractory to apomorphine but also has a considerable elevation in the emetic threshold to copper sulfate.

COMMENT

It is generally agreed that the central coordinating control for vomiting has not yet been convincingly localized to any circumscribed area in the brain stem. This may be explained by the consistent failure in the past to produce emesis to direct electrical stimulation of the medulla and also by the inability to eliminate or permanently impair the emetic response in chronic experimental animals. Consequently, authors of textbooks of neuroanatomy and neurophysiology are not in accord

in designating a specific structure as the vomiting center; for example, Tilney and Riley [17] designate special subdivision of the dorsal motor nucleus of the vagus, and Mettler,[18] the nucleus of Roller.

In the decerebrate preparation, the central mechanism for vomiting is not depressed as with pentobarbital anesthesia, and emetic responses can be obtained repeatedly when the region corresponding to the tractus solitarius and its nucleus and the dorsolateral border of the lateral reticular formation is stimulated electrically. It is of interest to note that the responsive region is not limited to a single neuroanatomic unit and that it is situated in the midst of other loci, the activities of which are integral parts of the physiologic pattern of vomiting, namely, salivation,[19] spasmodic respiratory movements [7] and forced inspiration.[20] This anatomic proximity reaffirms the idea that the vomiting center is a coordinating mechanism.

After ablation of the region of the medulla responsive to stimulation, dogs showed pronounced refractoriness to both apomorphine and copper sulfate. This is in contrast to the behavior of animals with more superficial lesions placed in the region of the dorsal nucleus of the vagus, which showed great disparity in the altered response to the two emetic agents. The increase in the threshold to copper sulfate was indeed slight. A pertinent question which is likely to arise in the analysis of results of this nature is why the response to copper sulfate was not completely eliminated by the deep lesion technic. To this, the most likely explanation is that the vomiting center in these animals, such as dogs 12 and 183, is not totally excluded. It is of interest that copper is a strong systemic poison and that it is extremely difficult to interfere peripherally with emetic stimuli due to a concentrated copper sulfate solution; even animals in which all afferent pathways from the gastrointestinal tract had been severed vomited on the administration orally of 320 mg. of copper sulfate (unpublished data). Recent work in this laboratory indicates that copper at sufficiently high levels in the blood may cause emesis by a central action. In the placing of the deep lesion in the medulla the area to be destroyed is in such close proximity to regions regulating the vital functions that one becomes extremely dubious of the possibility of maintaining an animal with total abolition of the mechanism for reflex emesis to copper sulfate.

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17. Tilney, F., and Riley, H. A.: The Form and Functions of the Central Nervous System, ed. 3, New York, Paul B. Hoeber, Inc., 1938, p. 267.

18. Mettler, F. A.: Neuroanatomy, ed. 2, St. Louis, C. V. Mosby Company, 1948, p. 278.

19. Wang, S. C.: Localization of the Salivatory Center in the Medulla of the Cat, J. Neurophysiol. **6**:195-202, 1943.

20. Pitts, R. F.; Magoun, H. W., and Ranson, S. W.: Localization of the Medullary Respiratory Centers in the Cat, Am. J. Physiol. **126**:673-688, 1939.

Recently, however, we have used gold or glass radon seeds for local tissue destruction in the medulla and have successfully inserted them in the desired location by approaching it through the cervical

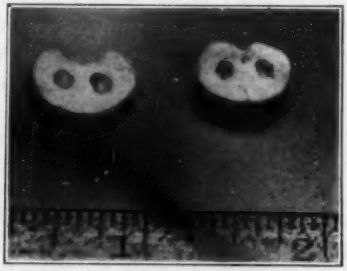

Fig. 5.—Cross section of medullary lesions made by glass radon seeds (left, mainly beta radiation) and by gold radon seeds (right, mainly gamma radiation). Note the well circumscribed nature of the lesion. The dog with glass seeds survived ten days; the dog with gold seeds, eleven days.

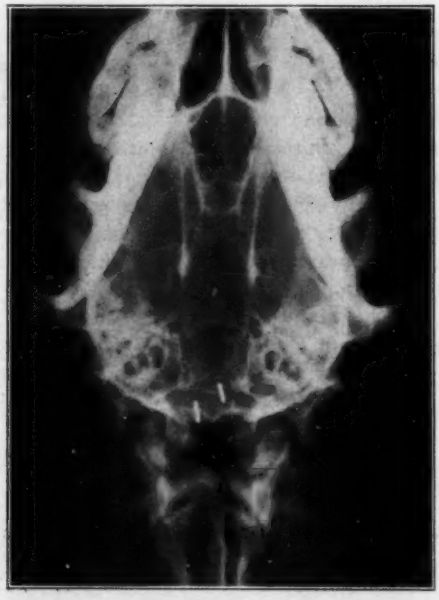

Fig. 6.—Roentgenogram of the skull of dog 106. Note the gold radon seeds implanted in the medulla oblongata.

flexure of the spinal cord. Circumscribed lesions produced with this technic are shown in figure 5. Dog 106, which survived for twenty-nine

days with implanted gold seeds (fig. 6), showed a decided increase in threshold to apomorphine, as well as to copper sulfate. In fact, this dog was completely refractory to 320 mg. of copper sulphate (eight times the preoperative threshold) but died four hours after oral administration. This work is still in progress.

From the data on the two series of chronic ablation experiments, we may conclude that the vomiting center resides in deep structures of the medulla oblongata and that the dorsal sensory nucleus of the vagus, claimed by Hatcher and Weiss [5] to be the vomiting center, is only an afferent station on which the central emetic, apomorphine, acts.

SUMMARY AND CONCLUSIONS

The location of the vomiting center in the brain stem was demonstrated by two basic methods:

1. Electrical stimulation of a certain region of the medulla elicited vomiting. This reactive region corresponds to the dorsolateral border of the lateral reticular formation, including the tractus solitarius and its nucleus.

2. Destruction of the same general region produced a preparation which was permanently refractory to high doses of apomorphine and copper sulfate. On the other hand, animals with bilateral ablation of the dorsal nucleus of the vagus, while also permanently refractory to apomorphine, responded reflexly to small doses of copper sulfate. The dorsal sensory nucleus of the vagus, on which apomorphine acts, thus constitutes one of the afferent influences on the emetic neuron complex.

Therefore, the central mechanism of vomiting per se must reside in the dorsolateral border of the lateral reticular formation and not in the superficial structures designated by Hatcher and Weiss.[5] This center is in the midst of other loci, the activities of which constitute the complex physiologic pattern of vomiting.

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SPONTANEOUS THROMBOSIS OF THE CAROTID ARTERIES IN THE NECK

Report of Four Cases

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DETROIT

NEUROLOGIC abnormalities following a "cerebrovascular accident" or "stroke" are generally regarded as manifestations of intracranial vascular disease. It is seldom appreciated that the same picture may be associated with occlusion of the main arterial pathways in the neck.

Interest in this occurrence was recently stimulated by our encountering 3 cases in which the common, external and internal carotid arteries on one side were found to be occluded completely by a thrombus and 1 case with thrombosis of the internal carotid artery (tables 1, 2 and 3). During the initial period of observation the patients were considered to have intracranial cerebrovascular disease. The rarity of this syndrome may be due in part to the fact that clinical and pathologic examination of the large vessels in the neck is usually overlooked. One purpose of this report is to urge routine examination by palpation and by operative exposure, when indicated, of the cervical portion of the carotid arteries in patients presenting evidence of cerebrovascular disease.

Thromboses of the cervical portion of the carotid arteries secondary to, or associated with, trauma,[1] local disease [2] in the neck and aneurysm [3]

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Read at the Seventy-Fourth Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 13, 1949.

From the Department of Surgery, Wayne University College of Medicine; the City of Detroit Receiving and Dearborn Veterans Administration Hospitals, and the Department of Neurosurgery, Grace Hospital.

1. Caldwell, J. A.: Post-Traumatic Thrombosis of Internal Carotid Artery, Am. J. Surg. **32**:522-523 (June) 1936. Greco, T.: Carotid Thrombosis Caused by Neck Injury: Report of a Case and Review of Literature, Arch. ital. di chir. **39**:757-784, 1935.

(Footnotes continued on next page)

have been described. The pathogenic sequence in these instances requires little comment. Less frequently have cases of spontaneous thrombosis of these vessels been recorded in the absence of specific local or systemic disease. Recent reports on this subject have dealt with examples of

TABLE 1.—*Data on Cases of Thrombosis of the Carotid Arteries in the Neck*

Case No.	Age, Yr.	Duration	Neurologic Status	Blood Pressure	Ocular Findings	Condition on Follow-Up Study
1	24	4 mo.	Left hemiparesis	100/70	Right optic nerve atrophy	No change
2	71	3 mo.	Right hemiparesis; aphasia	150/100	.....	No change
3	63	2 yr.	.....	230/130	Left optic nerve atrophy	No change
4	52	1 wk.	Right hemiparesis; aphasia	200/110	.....	Improvement 2 mo. later

TABLE 2.—*Visual Disturbances in Cases of Thrombosis of the Carotid Arteries in the Neck*

Case No.	Fundus		Vision		Neurologic Status	Age, Yr.
	Right	Left	Right	Left		
1	Optic nerve atrophy	.....	Blindness	Loss of temporal field	Left hemiplegia	24
3	.....	Optic nerve atrophy	Normal	Loss of inferior and temporal field	No paralytic phenomena	63

TABLE 3.—*Electroencephalographic Findings in Cases of Thrombosis of Carotid Artery in the Neck*

Case No.	Duration of Symptoms	Electroencephalographic Record	Artery Thrombosed
1	8 mo.	Voltage reduction, right hemisphere	Right common, internal and external carotid
2	3 mo.	Delta 1-2/sec., left hemisphere	Left common, internal and external carotid
3	4 mo.	Normal	Left common, internal and external carotid
4	1 wk.	Delta 1-2/sec., left hemisphere; improvement 2 mo. later	Left internal carotid

2. Brandberg, R.: Tumor of Carotid Body with Thrombosis of Arteria Carotis Interna, Acta chir. scandinav. **65**:464-474, 1929. Litchfield, H. R.: Arterial Thrombosis Complicating Retropharyngeal Abscess, Arch. Pediat. **55**:36-41 (Jan.) 1938.

3. Darling, S. T., and Clark, H. C.: Arteritis Syphilitica Obliterans, J. M. Research **32**:1-26 (March) 1915. Aldrich, A. L.: Occlusion of the Left Common Carotid Artery, U. S. Nav. M. Bull. **22**:48-51 (Jan.) 1925.

thrombotic occlusion of the internal carotid artery.[4] Cases of this type have been presented by Erickson,[4a] Andrell,[4b] Wolfe[4c] and Chao and associates.[4d] The diagnosis in most of these cases was made by means of operative exposure for arteriography as occurred in our case 4. Kussmaul,[5] in 1872, described 2 cases of spontaneous and gradual occlusion of "the carotid artery." The specific vessels involved were not mentioned except for the comment that in 1 of the cases "the left common carotid artery was occluded and the external carotid artery was pulseless." Penzoldt,[6] in 1881, reported a case of sudden blindness, with the subsequent appearance of an atrophic optic disk and hemiplegia. Autopsy revealed thrombosis of the right common and internal carotid arteries with patency of the external carotid artery and a large area of softening in the right cerebral hemisphere. Primary spontaneous thrombosis of the common, external and internal carotid vessels is a rarer lesion. Galdston and associates[7] collected 11 cases of such a condition from the literature and contributed 2 others. In our report we add 3 cases with pathologic examination of the involved vessels.

REPORT OF CASES

CASE 1.—F. L. L., a 24 year old white man, a laborer, was admitted to the Dearborn Veterans Administration Hospital on Sept. 9, 1948, complaining of paralysis of the left arm and leg, blindness in the right eye and impairment of memory, all of approximately four months' duration. He stated that he had been in good health until the morning of May 15, 1948, when he awoke and found that he was unable to use his left arm and leg. At the same time he had severe frontal headache, which persisted for almost six weeks. Along with the inability to use the left upper and lower extremities, he noted diminished sensation in these limbs, impairment of memory and confusion. During the ensuing weeks he was seen by several physicians and was informed that he had had a "stroke." Early in the course of his illness he became aware of visual impairment while reading and was subsequently informed by a physician that he was "blind in the right eye." He gradually acquired restricted power with spasticity in the left upper and lower extremities.

4. (*a*) Erickson, S.: Ueber Arteriographie bei Thrombose in der Carotis interna, Acta radiol. **24**:392-402, 1943. (*b*) Andrell, P. O.: Thrombosis of the Internal Carotid Artery (A Clinical Study of 9 Cases Diagnosed by Arteriography), Acta med. scandinav. **114**:336-372, 1943. (*c*) Wolfe, H. R. I.: Unexplained Thrombosis of the Internal Carotid Artery, Lancet **2**:567-569 (Oct. 9) 1948. (*d*) Chao, W. H.; Kwan, S. T.; Lyman, R. S., and Loucks, H. H.: Thrombosis of the Left Internal Carotid Artery, Arch. Surg. **37**:100-111 (July) 1938. (*e*) Sorgo, W.: Ueber den. Art. carotis interna-Verschluss bei jüngeren Personen, Ztschr. f. d. ges. Neurol. u. Psychiat. **167**:581-585, 1939.

5. Kussmaul, A.: Zwei Fälle von spontaner, allmäliger Verschliessung grosser Halsarterienstämme, Deutsche Klin. **24**:461; 473, 1872.

6. Penzoldt, F.: Ueber Thrombose autochthone oder embolische der Carotis, Deutsches Arch. f. klin. Med. **28**:80-93, 1880-1881.

7. Galdston, M.; Govons, S.; Wortis, S. B.; Steele, J. M., and Taylor, H. K.: Thrombosis of the Common, Internal and External Carotid Arteries (Report of Two Cases with a Review of the Literature), Arch. Int. Med. **67**:1162-1176 (June) 1941.

Examination.—The patient walked with a typical spastic hemiplegic gait. Confirmatory signs referable to the pyramidal tract were present on the left side of the body. There was absence of pulsations in the right carotid and temporal arteries. The blood pressure was 90 systolic and 68 diastolic in each upper extremity. The right fundus revealed a pale, white disk with distinctly outlined margins (fig. 1). The arteries and veins were uniformly narrowed. The left fundus was normal. Visual acuity was 0/0 in the right eye and 20/20 in the left eye, with a left hemianoptic defect. Audiometric examination revealed 5 per cent loss of hearing in the right ear. Sensation was diminished in all modalities on the paralyzed side. A Wechsler-Bellevue intelligence test showed 13.7 per cent mental deterioration, and the findings on psychometric examination were "highly suggestive of an organic pathologic disturbance in the brain." The results of all laboratory tests, as well as roentgenograms and the electrocardiogram, were normal. The spinal

Fig. 1 (case 1).—Photograph of the right fundus, showing a pale optic disk. The patient had atrophy of the right optic nerve with signs referable to the pyramidal tract on the left half of the body.

fluid, except for a protein content of 57 mg. per hundred cubic centimeters, was normal.

Operation.—The right common carotid artery, as well as the internal and external branches, was exposed. The vessels were of normal size. The internal jugular vein was also normal in size. The common carotid artery did not pulsate and had the consistency of rubber. An 18 gage needle introduced into the common carotid artery did not yield blood, nor could saline solution be introduced into the vessel. This abnormality was present in both the internal and the external branch of the common carotid artery.

Further Course.—The patient was readmitted to the hospital on Feb. 7, 1949 because of an episode of syncope associated with "shaking," in the course of which he had bitten his tongue.

An electroencephalogram at this time revealed focal voltage suppression in the right occipital area. There was no associated delta activity. On March 18, the

right side of the neck was reexplored, and a segment of common carotid artery, including the bifurcation and short segments of the external and internal branches, was removed (fig. 2). Microscopic examination revealed advanced arteriosclerotic narrowing of the external carotid artery with organized thrombus of the common, internal and external carotid arteries (fig. 3).

Comment.—This case is one of thrombosis of the common, internal and external carotid arteries on the right side with homolateral optic nerve atrophy and contralateral spastic hemiplegia. The etiologic factor in the thrombosis was arteriosclerosis of the carotid vessels. No other factors were noted. In this case the thrombosis was of the explosive form, with sudden onset of symptoms and signs.

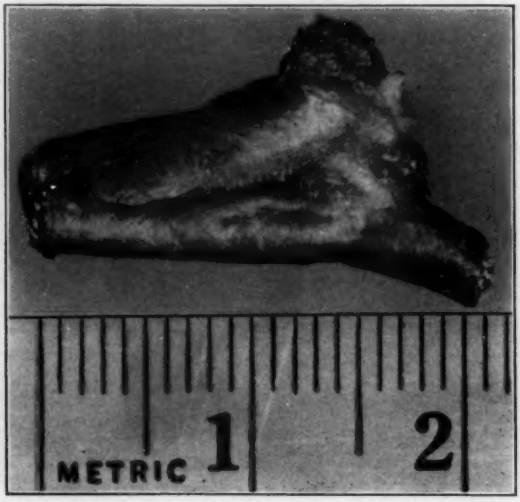

Fig. 2 (case 1).—Gross specimen of the common, internal and external carotid arteries. The vessels were of rubbery consistency and were completely occluded by an organized thrombus.

CASE 2.—G. S., a 71 year old white woman, a housewife, was admitted to Grace Hospital on Oct. 29, 1948. She had been in satisfactory health until July 24, 1948, when she suddenly lost consciousness while eating breakfast. When she had regained consciousness, it was noted that she was unable to speak and had "lost control" of the right upper extremity. "Vomiting spells" then developed, and she was hospitalized for a period of five days, during which time the vomiting ceased.

Examination.—The patient was unusually restless, tense and excitable. At times she uttered a lucid sentence. She presented a mixed type of aphasia. Her blood pressure was 150 systolic and 100 diastolic. The fundi were of normal appearance for a person of her age. There was no evidence of optic nerve atrophy, and the artery-vein ratio was normal. The visual fields were full. Pulsation of the left carotid artery was absent. Right hemiparesis of mild degree was present, associated with signs of involvement of the pyramidal tract. Astereognosis was present

in the right upper extremity. All laboratory findings were normal. Roentgenologic studies of the skull showed frontal hyperostosis with parasellar opacities resembling calcified deposits in the carotid artery. The electroencephalogram was "strongly suggestive of a local organic disturbance in the left temporal to left frontal area."

Operation.—The left common carotid artery was exposed, as well as the internal and external branches. The vessels were found to be firm, having a solid, rubbery consistency, and all pulsation was absent. The internal jugular vein appeared to be of nearly normal size. When an 18-gage needle was introduced into the lumen of the vessels, no blood could be withdrawn, nor could saline solution be injected. A section of the artery was then removed for pathologic study.

Microscopic examination of this vessel showed a moderately advanced degree of atherosclerosis and thickening of the intima, with a recently formed thrombus in the lumen (fig. 4).

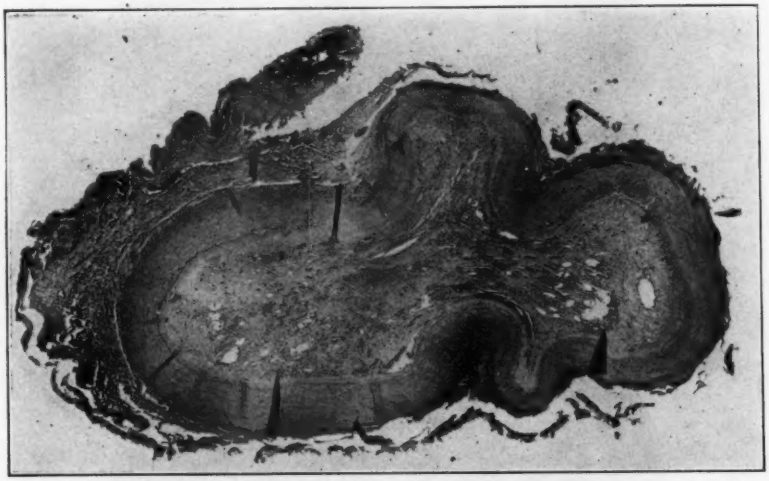

Fig. 3 (case 1).—Cross section of the bifurcation of the common carotid artery into its internal and external branches. Note the presence of a completely organized thrombus throughout the lumen of these vessels.

Comment.—This case is one of thrombosis of the carotid artery with sudden onset of paralysis involving the right side of the body and aphasia. The etiologic factor was atherosclerosis. It should be noted that no changes in the fundus were seen in this case, and vision and visual fields were normal for the patient's age.

CASE 3.—C. B., a 63 year old Negro, was admitted to the City of Detroit Receiving Hospital on Dec. 1, 1948, with the complaint of blurring of vision, which had become progressively worse during the previous four months. The blurring was greater in the right eye. He had also noted twitching of the left side of the face for approximately four months. His past history indicated that he had had hypertensive vascular disease for fifteen years, with several episodes of mild cardiac decompensation. He was formerly occupied as a Pullman porter.

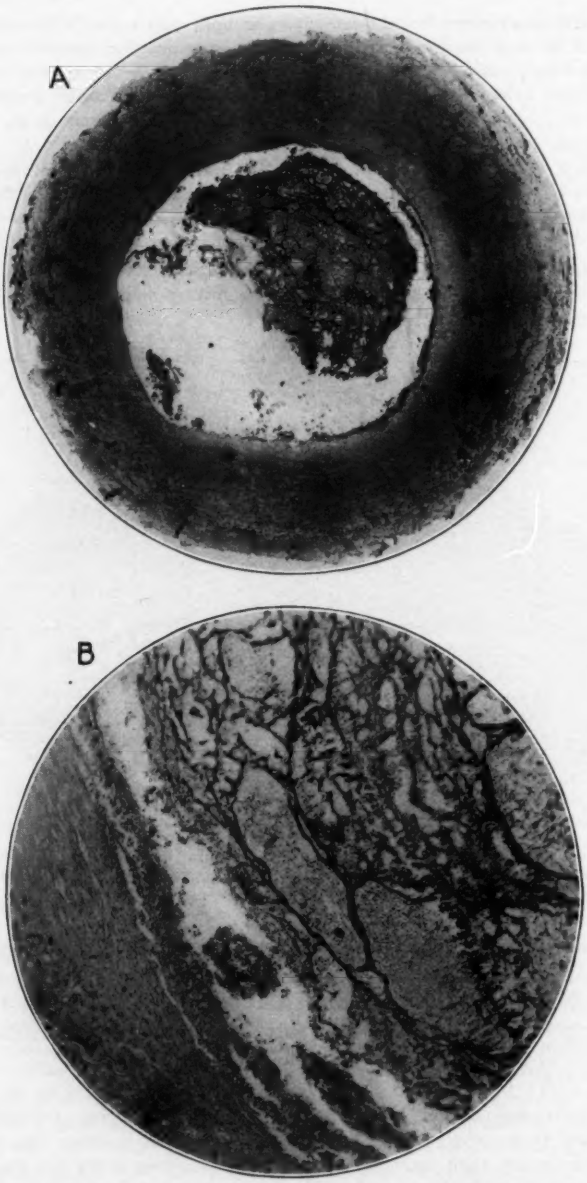

Fig. 4 (case 2).—*A*, cross section of the common carotid artery, showing an organized thrombus. *B*, greater magnification of the thrombosed vessel, showing organization and atherosclerosis.

Examination.—The patient was obese, weighing approximately 250 pounds (113.4 Kg.). There was twitching of the musculature about the left eye and cheek, with increased pigmentation of that side of the face. The right optic disk was normal in color, with normal cupping. The veins were dilated, the artery-vein ratio being 2:3, with slight arteriovenous compression. No hemorrhages were noted. The macular area exhibited some granular changes. The left optic disk was pale, with a moderate degree of cupping. The vessels, retina and macula were similar to those in the right eye. The right eye revealed normal peripheral fields with some enlargement of the blindspot. The left eye showed definite loss of most of the inferior field with contraction of the superior field. There was absence of the pulsations of the carotid artery in the left side of the neck. An electrocardiogram revealed sinus rhythm with left axis deviation and damage to the left ventricle.

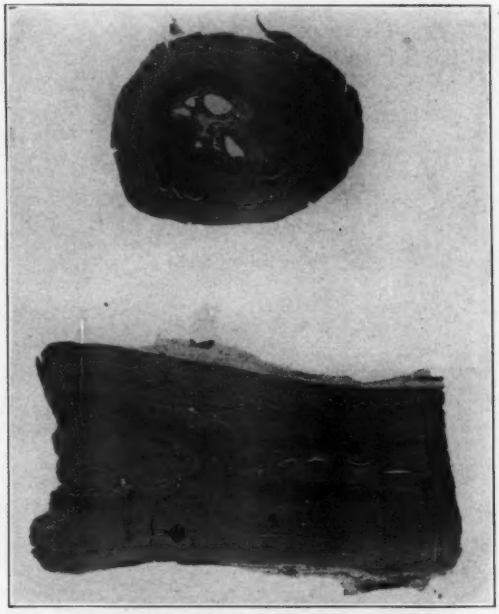

Fig. 5 (case 3).—Cross and longitudinal sections of the thrombosed carotid artery after removal of a segment. A large organized thrombus in the lumen of the artery can be seen.

Roentgenologic studies of the chest showed considerable hypertrophy of the left ventricle. All other laboratory findings were normal. The electroencephalogram was essentially normal.

Operation.—Exposure of the carotid artery and its component branches was made with the patient under general anesthesia. The jugular vein was enlarged to twice its normal size. The common carotid artery was firm and nonpulsatile throughout its extent, the artery having been well exposed through its course in the neck. The thrombosed branches of the artery were likewise exposed and palpated as far as possible to the base of the skull. A needle inserted into the vessels showed no evidence of returning blood. A section of the artery 2 cm. in

length was excised, and the ends of the artery were ligated. Microscopic examination showed marked atheromatous changes with organized thrombus occluding the lumen (figs. 5 and 6).

Comment.—Case 3 is one of carotid thrombosis with the main disability a visual disturbance. The patient showed atrophy of the left optic nerve with involvement of the visual field. There was no evidence of motor or sensory paralysis. It should also be noted that this patient's

Fig. 6 (case 3).—Photomicrograph showing the organized thrombus of the common carotid artery. The vessel wall presents atherosclerotic changes.

complaints developed gradually in contrast to the course in cases 1 and 2. In our classification, on the basis of the clinical manifestations, this case belongs to the form with visual disturbance.

Case 4.—M. C., a woman aged 52, became paralyzed in the right half of the body and also lost her power of speech ten days prior to her admission to Grace Hospital, on Feb. 5, 1949. She had hypertensive vascular disease, with a blood pressure of 200 systolic and 110 diastolic, and had been treated for four or five years.

Examination.—Examination revealed grade 2 changes in the retina bilaterally. The patient was aphasic with right hemiplegia. The spinal fluid was clear with normal pressure. Palpation of the vessels of the neck revealed pulsations on both sides. The pulsations of the temporal artery were also noted on both sides. The electroencephalogram showed a focus of delta activity in the left motor and temporal areas.

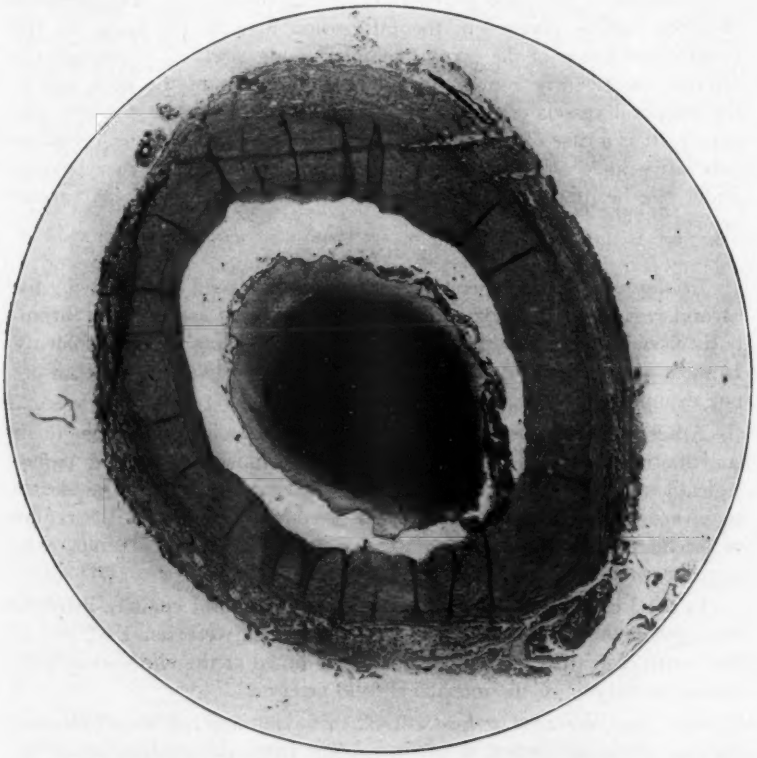

Fig. 7 (case 4).—Photomicrograph of the internal carotid artery, showing beginning organization of a recent thrombus. The vessel wall showed atherosclerosis.

Operation.—Operation for arteriography prior to anticoagulant therapy revealed a markedly atheromatous bifurcation of the common carotid artery with complete occlusion of the internal carotid artery. The thrombus must have been of recent origin, since an 18 gage needle introduced into the internal carotid artery yielded clotted material. The bifurcation of the carotid artery felt hard, and palpation suggested the presence of calcifying plaques.

A portion of the internal carotid artery was removed for biopsy, which revealed atheromatous change of the artery with intimal thickening and recent thrombosis (fig. 7).

Further Course.—The patient showed excellent improvement in her speech and her ability to move the right half of the body and was discharged four weeks later, able to walk by herself and able to carry on a conversation except for a "few mistakes." The electroencephalogram two months after her discharge revealed striking improvement in the pattern, although some abnormality could still be noted in the left temporal and parietal areas.

Comment.—This case is reported for two reasons: 1. The presence of atheromatous plaques in the bifurcation may be the basis for the eventual occlusion of the carotid complex in the neck. 2. Although the internal carotid artery was thrombosed, pulsations of the neck and of the temporal vessels could be felt, since the external carotid artery was patent. It is a case of this type in which an arteriography may reveal an "operative find." On the basis of the clinical picture, this case belongs under the heading of the explosive form of thrombosis of the carotid artery.

COMMENT

Etiology.—The pathogenesis of spontaneous thrombosis involving the carotid vessels may be related to the phenomenon of spontaneous thrombosis elsewhere in the body, and in that event presents similar problems. In most of the cases reported in the literature the involved vessels were not examined pathologically.

Atherosclerosis has been the most commonly invoked etiologic or contributing factor. In those specimens which were examined pathologically this alteration has been noted. Atherosclerosis of a moderate to severe degree has been reported as a common finding in the region of the bifurcation of the common carotid artery and carotid sinus, even in young adults.[8]

In the 3 cases in this report advanced atheromatous changes involved the segments of the common carotid artery which were removed, and in the fourth case atheromatous plaques were noted at the bifurcation, with recent thrombosis of the internal carotid artery.

Age; Sex; Vessel Involved.—That this syndrome has no predilection for any particular period of life is evident from an examination of the age incidence in the reported cases. The ages have ranged from the first through the eighth decade of life, with a fairly equal and preponderant distribution in the third, fourth, fifth and sixth decades. The youngest patient was 7 and the oldest 71 years of age. The sex incidence, however, exhibited a preponderance in males, males having been affected oftener than females by a ratio of about 3.5 : 1.0. A much more striking

8. Keele, C. A.: Pathological Changes in the Carotid Sinus and Their Relationship to Hypertension, Quart. J. Med. **2**:213-220 (April) 1933. Dow, D. R.: The Incidence of Arteriosclerosis in the Arteries of the Body, Brit. M. J. **2**:162-163 (July 25) 1925. Hultquist, cited by Andrell.[4b] Poli and Zucha, cited by Erickson.[4a] Galdston and others.[7] Andrell.[4b]

correlation may be noted in the predilection of the thrombosis for the carotid vessels on the left side. The left side of the neck was involved approximately 6.5 times as frequently as the right. The significance of this occurrence may perhaps be related to the variation in the origin of the carotid arteries on the two sides, with differing hemodynamics and greater ease of embolism.

Clinical Findings.—The symptoms of the syndrome of primary carotid thrombosis is essentially that of the much more familiar "cerebrovascular accident," but in a significant number of cases of thrombosis of the carotid artery certain other features have appeared with a sufficient degree of regularity to make them worthy of note.

Headache was reported as a frequent premonitory symptom. Transient and recurrent neurologic prodromal signs appeared to be common in the cases reported, suggesting psychosomatic complaints. In a smaller number of cases the onset was explosive, presenting at the outset severe neurologic changes. In 3 of our cases, the onset was sudden, with no history of prodromal symptoms. A finding of particular interest in 2 of our cases was that of homolateral optic nerve atrophy.

It is known that the internal carotid artery may be ligated intracranially, as well as in its cervical portion, along with the external carotid artery, without producing blindness in the ipsilateral eye. Adequate collateral circulation occurs from the contralateral vessels via the anterior communicating artery; however, when thrombosis extends all the way to the ophthalmic artery, this collateral supply may not be available, and an acute visual loss with optic nerve atrophy may ensue. Actual direct compression of the optic nerve by the thrombosed ophthalmic artery may account for delayed atrophy of the nerve in other instances.

The final proof of the diagnosis must depend on exposure of the vessels.

SUMMARY

Three cases of spontaneous thrombosis of the common, external and internal carotid arteries and 1 case of thrombosis of the internal carotid artery are presented.

The diagnosis may be made by palpation of the neck and of the temporal arteries.

The clinical types of thrombosis of the carotid vessels in the neck are four: (1) the explosive form, simulating the usual cerebrovascular accident; (2) the slowly progressive form, with neurologic symptoms of varying severity; (3) the form having a visual disturbance, with associated homolateral blindness and optic nerve atrophy, and (4) the silent form, with no disabling symptoms or signs.

In our cases a microscopic study of the thrombosed vessels indicated that atherosclerosis was the important etiologic factor.

PAIN AND CONTRACTURE IN POLIOMYELITIS

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THE PATIENT with acute poliomyelitis is often much more concerned with the pain of the disease than he is with the paralysis. Patients have been known to remain awake for an entire week as a result of the pain, yet, despite the importance of this symptom in poliomyelitis, little is known of its cause. One of us (A. C. G.)[1] was the victim of a severe attack of poliomyelitis in 1946. Since that time animal experiments, to be described in the present paper, have been conducted in an attempt to correlate experimentally induced lesions with the sensory disturbances of the disease.

Clinicians have known for many years that there are several types of pain in poliomyelitis.[2] In the early stages of the acute disease the patient usually has severe headache. At the same time he has severe pain in the lower part of the back, and he may complain of hyperesthesias of the skin, which may or may not be painful. After approximately a week of the acute disease process, the temperature goes down, the headache subsides, the hyperesthesias disappear and the patient is left with some low backache and with severe muscular pain, which is greatly aggravated by movement, pressure and stretching. It is the last type of pain, muscular pain, which causes the patient his greatest discomfort, and it is to this pain that one generally refers when one speaks of the pain of poliomyelitis.

The muscular pain of poliomyelitis has been effectively described as similar to that which occurs on the day after an extreme bout of exercise.[3] It may further be described as the sensation of a stiff neck

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1. Guyton, A. C.: Reaction of the Body to Poliomyelitis and the Recovery Process, Arch. Int. Med. **83**:27 (Jan.) 1949; Relation of Symptoms to the Pathological Physiology in Poliomyelitis, J. Tennessee M. A. **41**:254 (July) 1948.

2. Fry, F. R.: Acute Anterior Poliomyelitis in a Youth of 18 Years; Remarks on the Sensory Symptoms, J. A. M. A. **38**:1357 (May 24) 1902.

3. Buchthal, F.: Problems of the Pathologic Physiology of Poliomyelitis, Am. J. Med. **6**:579 (May) 1949.

the morning after one has slept in a cold breeze and also as that following a severe muscular bruise. These conditions have been experienced by most persons at one time or another. In all such conditions, as well as in poliomyelitis, when the muscle is pressed, the subject feels a severe, sharp pain deep in the muscle. Likewise, when the stiff neck is turned or a sore hamstring muscle is stretched, the patient again feels the sharp pain. Between the periods in which sharp pain is evoked, the muscles may be completely comfortable if the condition is mild; but if it is severe, there results a steady, dull, aching pain. Consider for a moment the patient with poliomyelitis as experiencing precisely the same severe soreness, but this time in all his muscles—not merely in a few. There is no such thing as getting off the sore muscles by turning in the bed, for the next muscle is as sore as the first. Moreover, the soreness is often as severe as though each muscle of the body had been selectively pounded with a hammer. Therefore, considering the degree of soreness, as well as its extent through the body, even the physician who has never had poliomyelitis himself may possibly be able to comprehend the severity of the pain associated with the disease.

Contracture is also a problem with the patient with poliomyelitis though of less early concern. Obviously, if this could be prevented, much of the after-treatment of the disease would be obviated. Here, again, as in the case of pain, if more were known about the cause of contracture in poliomyelitis, treatment might possibly be improved.

EXPERIMENTAL STUDIES ON PAIN OF POLIOMYELITIS

It was the purpose of the present study to induce in human and in animal subjects the same type of pain as that found in poliomyelitis. The pain was induced by two methods: production of ischemia in both dogs and human subjects, and section of the anterior roots of the spinal cord in dogs with preservation of the posterior roots from the same segments.

A. Pain Induced by Ischemia.—A special electronic apparatus was built which controls the inflation and deflation of a blood pressure cuff automatically.[4] This inflates the cuff for a predetermined period of from one second to three minutes; then it suddenly deflates it for a predetermined period of from one second to three minutes, after which it repeats the cycle indefinitely. Thus, the blood flow to a limb may be completely halted for a given period during each cycle, and the blood flow to the limb can be quantitated in terms of the percentage of time that the blood is allowed to flow.

4. Guyton, A. C., and Miller, G. L.: Apparatus for Producing Quantitative Ischemia in the Limbs of Animals, J. Lab. & Clin. Med. **33**:1450 (Nov.) 1948.

In the arms of 7 human volunteers using a total cycle averaging one and one-half minutes, we found that blood flow must be completely occluded for approximately 95 per cent of the time in order to produce pain. We further found that exercise of the muscle during the experiment caused pain when the period of occlusion was only 85 per cent of the time, or even less, depending on the vigorousness of the exercise. Immersion of the arm in cold water slightly increased the degree of pain, and immersion in warm water slightly decreased it.

The nature of the pain in human subjects, though difficult to characterize, was not that of poliomyelitis, with its sore muscles, but, as was to be expected, was that commonly ascribed to Raynaud's and Buerger's disease (thromboangiitis obliterans). The pain began with a dull ache, which crescendoed into a sharp and penetrating ache, such as that normally experienced as the result of a bunion or a plantar wart.

Nine dogs, very lightly anesthetized with pentobarbital sodium, were subjected to ischemia of one foreleg for an average period of eight hours. Because of the lightness of the anesthesia, the animals had a natural tendency to wail when they felt pain. This reaction proved to be a satisfactory end point for the experiment, for the results could be easily duplicated. Cycles of blood flow and cessation of flow, ranging from thirty seconds to five minutes, were studied. When the blood was cut off for more than three minutes at any one time, regardless of the duration of blood flow between the periods of cessation of flow, the animals would wail with pain. When the cycles were kept short, from one to one and one-half minutes, the development of pain depended on the percentage of time that the blood flow was cut off. It was found that wailing invariably occurred when the blood flow was cut off from 90 to 95 per cent or more of the time. Wailing ceased immediately when more blood was allowed. At the end of the eight hour periods, the muscles did not appear to be tender to pressure, as judged by attempts to produce wailing. There was, however, a slight limitation of motion in the ankle joint associated with moderate edema, which was considered to be the cause of limited motion. Sixteen hours after the eight hour period of 95 per cent cessation of blood flow, the legs appeared to be completely normal.

In 5 dogs, unilateral ligation of the femoral artery in the femoral triangle failed completely to produce any postoperative tenderness, pain or contracture. In the same dogs, in order that most of the collateral circulation might be obstructed, the common iliac arteries on the same side were ligated an average of five days later. Here, again, the results were not significant.

B. Pain and Contracture Caused by Anterior Rhizotomy.—The only surgical lesion which can approximate the pathologic lesion of poliomye-

litis is anterior rhizotomy. Such a lesion causes death of the peripheral motor nerve with consequent muscular paralysis and atrophy. Unfortunately, the efferent sympathetic fibers are also destroyed; on the other hand, fortunately for the studies on pain, the posterior roots are uninvolved and may well transmit pain from the muscles. Such is not true when the entire nerve is cut.

In a series of 25 dogs in which the anterior roots were sectioned at approximately the third, fourth and fifth lumbar segments on the right side, the right leg showed postoperative pain and contracture, which may be characterized as follows: The anterior muscles of the thigh and the anterior flexors of the foot exhibited the greatest degree of paralysis, and usually were completely paralyzed. From the second day until the fifth to the fifteenth day after operation the animal exhibited signs of extreme pain whenever the affected muscles were pressed, and most of the animals would scream and snap at the observer. Yet pressure on muscles of the control leg did not produce any response. Contracture began on approximately the fourth postoperative day and increased progressively until the end of the experiment, the longest postoperative period being thirty-nine days. Any attempts to stretch the contracted muscle back to its normal length caused the same vicious response from the animal as that described for pressure. The pain response to stretch, however, was much greater in the early days of the contracture, even before much contracture had developed, than it was a week or so later. Most of the contracture developed in the hamstring and gastrocnemius muscles. Plaster of paris casts on the legs of 5 animals for an average period of two weeks moderately increased the degree of contracture.

Because of the painful condition of the legs, studies on blood flow could not be made, but it was the clinical impression from the leg temperatures that there was no significant deviation from normal flow. Likewise, there was no development of edema. The mass of the paralyzed muscles decreased progressively during the experiment to reach approximately two thirds normal at the end of a month.

Fourteen of the animals were killed at intervals between the second and the thirty-ninth day after operation. Sections were removed from the sciatic nerve of the right leg, from one of the paralyzed muscles of the right leg, from the sciatic nerve of the left (control) leg and from a normal muscle of the control leg. The nerves and muscles were stained with hematoxylin and eosin, and Marchi stains were also made of the nerves. In general, little constructive information was obtained from the pathologic studies. Mildly stained, degenerating nerve fibers were observed with the Marchi stain, but there was no other evidence of edema, fibrosis or autolysis within the nerves. The muscle fibers from

atrophying muscles twenty-five days after operation and thereafter showed definite decrease in fiber size, associated with a relative increase in the number of nuclei. Also, the cross striations had begun to fade at this time, and the first evidence of fibrosis between the fibers had begun to appear. Before twenty-five days, however, no definite pathologic process could be conclusively demonstrated to account for the pain and contracture, which had begun very early.

COMMENT

The similarity of the symptoms in dogs which have had their anterior spinal nerve roots sectioned to those of lesions of acute poliomyelitis is striking. As could best be judged, the animals presented typical poliomyelitic pain with exquisite muscular tenderness to deep pressure and to stretch. The development of contracture also followed the same course as that usually presented in poliomyelitis, beginning with a plastic, but painful, resistance to stretch and ending with a nonpainful, but very solid, contracture, in which the muscles could not be stretched without tearing the muscle fibers.

There was, however, one definite difference between the muscular tenderness of poliomyelitis and that of the experimental animals: The pain in the animals lasted only five to ten days, instead of the weeks usually noted in severe cases of human poliomyelitis. Two factors must be considered in the possible explanation of this difference: First, the sympathetic fibers were cut in the present experiments, whereas in poliomyelitic patients not only are the sympathetic fibers still intact, but there is also much evidence that they are greatly hyperactive, with resultant vasoconstriction.[5] It is well known that a poor blood supply causes a great delay in the lysis of most abnormal cellular conditions, a fact which may well account for the long duration of pain in poliomyelitis. Second, the animals in the present experiments were allowed to move about freely, a condition which resulted in self-induced physical therapy. This undoubtedly aided the blood flow to the limbs, with resultant decrease in pain.

5. (*a*) Collins, V. J.; Foster, W. L., and West, W. J.: Vasomotor Disturbances in Poliomyelitis, with Special Reference to Treatment with Paravertebral Sympathetic Block, New England J. Med. **236**:694 (May 8) 1947. (*b*) Lannon, J., and Braude, J. L.: Muscle Spasm in Poliomyelitis: Its Treatment and Suggested Etiology, South African M. J. **23**:30 (Jan.) 1949. (*c*) Smith, E.; Rosenblatt, P., and Limaure, A. B.: The Role of the Sympathetic Nervous System in Acute Poliomyelitis: Preliminary Report, J. Pediat. **34**:1 (Jan.) 1949. (*d*) Smith, E.; Graubard, D. J.; Goldstein, N., and Bikoff, W.: A New Method in the Management of Acute Anterior Poliomyelitis, New York State J. Med. **48**:2608 (Dec. 1) 1948.

The fact that many methods of producing vasodilation, such as the use of heat, benzazoline (priscoline®; 2-benzyl-4.5-imidazoline hydrochloride),[5d] tetraethylammonium ion,[5b] neostigmine[6] and sympathetic block,[7] will relieve the pain of poliomyelitis has led many observers to propose sympathetic involvement as the cause of the pain. The pain which is caused by ischemia, however, is quite different from that of the sore muscles of poliomyelitis. Furthermore, results in the present experiments indicated that the degree of ischemia necessary to cause pain is far greater than could reasonably be expected to occur in poliomyelitis. This is particularly so when one considers the fact that blood vessels to muscles are relatively nonsusceptible to sympathetic impulses.[8] Furthermore, plethysmographic studies on paralyzed limbs have failed to reveal any notably deficient blood supply to the muscles.[9] Still another argument against the vasospastic origin of the pain is the fact that vasospasm is often a permanent sequela of poliomyelitis, but the pain lasts only a short while. Therefore, the probable relationship of vasospasm in poliomyelitis to the pain is merely to cause intensification and prolongation of the pain, even though the actual cause of the pain is another morbid condition.

What, then, is the cause of pain in poliomyelitis? The same question can be asked concerning pain in the stiff neck after one has been sleeping in a breeze, or the pain in a severely bruised muscle, in sore muscles after exercise and probably also in the sore muscles following anterior rhizotomy. What happens in the stiff neck syndrome is not known, but in all the other conditions mentioned, including poliomyelitis, there occur abnormal processes within the muscle fibers, as evidenced by decreased creatinine excretion in poliomyelitis,[10] muscular hypertrophy after exercise, atrophic processes after poliomyelitis and anterior rhizotomy and pathologic evidence of fiber injury following a bruise. Thus, in each of the conditions there is reason to believe that abnormal breakdown products are present in the muscle fibers which may very likely be the cause of pain. Furthermore, the poorer the circulation, the more intense will be the pain and the longer it will last.

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6. Watkins, A. L., and Brazier, M. A. B.: Observations on Muscle Spasm in Poliomyelitis, Arch. Phys. Med. **27**:328 (June) 1945.

7. Collins and others.[5a] Lannon and Braude.[5b]

8. White, J. C., and Smithwick, R. H.: The Autonomic Nervous System, ed. 2, New York, The Macmillan Company, 1941, p. 85.

9. Abramson, D. I.; Flachs, K.; Freiberg, J., and Mirsky, I. A.: Blood Flow in Extremities Affected by Anterior Poliomyelitis, Arch. Int. Med. **71**:391 (March) 1943.

10. Magers, E. J.: A Study of Certain Phases of Metabolism in Poliomyelitis, J. Biol. Chem. **105**:lvi (May) 1934.

There is no occasion to ascribe the muscular pain of poliomyelitis to lesions in the sensory nervous system, for a number of reasons. First, the lesions in these regions are few.[11] Second, destructive lesions in the central nervous system, such as those of poliomyelitis, almost invariably cause loss of sensation if the cells are killed. Because it is rare, if ever, that sensory impairment occurs after poliomyelitis, it is also to be doubted that lesions in the sensory nervous system could cause the prolonged muscular pain of poliomyelitis. Third, the pain of poliomyelitis is usually not present, except in the form of a dull ache, unless the muscle is pressed or stretched, thus indicating a purely local origin of pain in the muscle itself.

The pains of poliomyelitis, in addition to the muscular soreness, can, on the other hand, be explained best at present by abnormalities within the central nervous system associated with the acute disease. Headache often precedes paralysis by several days and leaves at the same time that the temperature returns to normal, approximately one week after the onset of paralysis. This symptom is, therefore, clearly associated with the disease process, probably owing to edematous pressure on the meninges, or possibly to meningeal irritation, and the reason that headache precedes paralysis is that the disease process usually passes through the brain several days prior to its progression into the spinal cord.[12]

The general tenseness which often precedes the onset of paralysis, and which coexists with it for several weeks, has been explained on the basis of lesions in the inhibitory centers of the hindbrain.[13] In other words, the neurons which normally inhibit the vestibular nuclei and other postural nuclei are destroyed, and the postural nuclei, particularly those controlling the antigravity muscles, overact, with resultant muscular tenseness. This possibly gives rise to the stiff and painful back, the nuchal stiffness and all the other symptoms commonly known as the meningeal symptoms of poliomyelitis. Meningeal inflammation is minor in poliomyelitis; therefore it is doubtful whether it could play a major role in the causation of symptoms.[14]

The cause of hyperesthesias of the skin is difficult to ascertain, and probably much of the hyperesthesia is merely anticipation on the part

11. Bodian, D.: Histopathologic Basis of Clinical Findings in Poliomyelitis, Am. J. Med. **6**:563 (May) 1949.

12. Howe, H. A., and Bodian, D.: Neural Mechanisms in Poliomyelitis, New York, Commonwealth Fund, 1942.

13. Bodian, D.: Experimental Evidence on the Cerebral Origin of Muscle Spasticity in Acute Poliomyelitis, Proc. Soc. Exper. Biol. & Med. **61**:170 (Feb.) 1946.

14. Buchthal.[3] Bodian.[11]

of the patient that the examiner, when he first touches the skin, may suddenly dig deeper into the sore muscle. Furthermore, there is probably some local sensory facilitation in the spinal cord, due to the coexisting impulses already arriving from the painful muscles. This is analogous to the concept of facilitation in referred pain from the viscera.[15] Yet there is another type of hyperesthesia, as well as paresthesia, which often precedes paralysis. To explain this, the personal experience of one of us (A. C. G.) must be described. Five days before paralysis, and two days before headache, several segmental areas of paresthesia resembling the pricking of pins, but not painful, developed at different points over the abdomen and chest. These continued uninterruptedly until the onset of paralysis but disappeared at about that time. Because it has been shown that once the virus invades the spinal cord its progress is rapid, it is necessary to invoke a lesion of the central nervous system to explain the development of this symptom so long prior to paralysis. A lesion in the thalamus, in which lesions are often found,[11] and in which sensory terminations from the periphery are segmentally arranged, would aptly explain the paresthesias. Here, then, is the one instance in which lesions of the nervous system probably directly cause sensory abnormalities, though not painful and lasting only a few days.

The contracture of poliomyelitis appears to be a simple result of atrophy, immobility and, later, fibrotic invasion. Shortening of muscle is a natural phenomenon which occurs in muscles immobilized in a shortened condition, and there is no reason to believe that the process in poliomyelitis is any different. There are a number of exaggerating influences in poliomyelitis, however. First, because of pain, there is an increased tendency for the patient to keep a muscle in the immobilized position. Second, the antagonistic muscle is often paralyzed, so that it is impossible to stretch a muscle which is undergoing the process of shortening. Third, the poor blood supply of muscles in poliomyelitis favors autolysis of muscle fibers and the growth of fibroblasts, which require little nutrition. Fourth, the atrophic process in the muscle fiber means a shrinkage in dimensions, which undoubtedly is linear, as well as horizontal.

There is no reason to implicate neurogenic spasm as a cause of contracture or pain, for in anterior rhizotomy, after which no neurogenic spasm could possibly exist, both contracture and pain occurred much the same as that which normally develops in poliomyelitis. Furthermore, in poliomyelitic patients, totally paralyzed muscles, from which no action potentials can be recorded, are subject to precisely the same type of contracture and pain as are those muscles which are still partially

15. Fulton, J. F.: Physiology of the Nervous System, ed. 2, New York, Oxford University Press, 1943, p. 10.

innervated.[1] Electromyographic evidence likewise indicates that the amount of spontaneous neurogenic stimulation of muscles during the acute disease, except when a pain reflex is evoked, is so slight that one is usually unable to determine whether or not it exists by clinical examination.[16] Therefore, the concept of neurogenic spasm as a cause of contracture and pain in poliomyelitis [17] appears to be totally unfounded.

In the treatment of the poliomyelitic muscle, except possibly for electrical stimulation,[18] there is no means by which the atrophic process can be prevented. Therefore treatment is strictly symptomatic and revolves around vasodilation and stretching of the paralyzed muscle. The vasodilation may be produced by any one of the methods noted. Even curare has a histamine effect [19] and may derive some of its benefit from this property. How vasodilation aids the muscle in poliomyelitis is difficult to determine, but certainly it is similar to the benefit observed in other types of muscular soreness—probably the removal of degenerative products and their replacement by new materials. Muscle stretching is merely the mechanical counterpart of the exaggerated shortening process of poliomyelitis already described, and there is no difficulty in understanding the benefit of stretching in preventing contracture, for it is well known that any person can become double jointed by the same process if he so desires.

SUMMARY

On the basis of personal experience of one of us (A. C. G.) and of his contacts with other patients, the pain of poliomyelitis is described as that commonly observed after a muscle bruise or after severe exercise, or that of a stiff neck after one has been sleeping in a cold breeze.

16. Buchthal.[8] Watkins, A. L.: Electromyographic Studies in Poliomyelitis, Journal-Lancet **64**:233 (July) 1944. Watkins, A. L.; Brazier, M. A. B., and Schwab, R. S.: Concepts of Muscle Dysfunction in Poliomyelitis, J. A. M. A. **123**:188 (Sept. 25) 1943. Schwartz, R. P.; Bouman, H. D., and Smith, W. K.: The Significance of Muscle Spasm in the Acute State of Infantile Paralysis Based on Action Current Records, J. A. M. A. **126**:695 (Nov. 11) 1944. Bouman, H. D., and Schwartz, R. P.: The Degree, the Extent, and the Mechanism of Muscle Spasm in Infantile Paralysis, New York State J. Med. **44**:147 (Jan. 15) 1944.

17. Kenny, E.: Treatment of Infantile Paralysis in the Acute Stage, Minneapolis, Bruce Publishing Company, 1941. Ober, F. R.: Pain and Tenderness During the Acute Stage of Poliomyelitis, J. A. M. A. **120**:514 (Oct. 17) 1942. Ransohoff, N. S.: Treatment of Acute Anterior Poliomyelitis with Curare and Intensive Physical Therapy, Bull. New York Acad. Med. **23**:661 (Nov.) 1947.

18. Solandt, D. Y.: Atrophy in Skeletal Muscle, J. A. M. A. **120**:511 (Oct. 17) 1942. Solandt, D. Y.; De Lury, D. B., and Hunter, J.: Effect of Electrical Stimulation on Atrophy of Denervated Skeletal Muscle, Arch. Neurol. & Psychiat. **49**:802 (June) 1943.

19. Grob, D.; Lilienthal, J. L., Jr., and Harvey, A. M.: On Certain Vascular Effects of Curare in Man: The "Histamine" Reaction, Bull. Johns Hopkins Hosp. **80**:299 (June) 1947.

Experimental studies on ischemic pain in the arm of human subjects suggest that this type of pain is not the same as that of poliomyelitis.

Studies on ischemia in the legs of dogs, as well as in the arms of human subjects, showed that blood flow must be stopped 90 to 95 per cent of the time in order that pain may be produced. There is no evidence that this degree of ischemia exists in the muscles in poliomyelitis.

In 25 dogs, anterior rhizotomy, a type of lesion physiologically resembling the lesion of poliomyelitis, invariably caused extreme sensitivity in the affected leg. Contracture, typical of that seen in poliomyelitis, also followed. It is concluded, therefore, that the pain and contracture in poliomyelitis are probably due to local pathologic changes in the muscle following denervation.

It is postulated that the pain of poliomyelitis may be caused by products of cellular degeneration and that the value of vasodilation in the treatment of this symptom is the increased removal of such products.

Neurogenic spasm as a cause of contracture and pain is discussed, and it is concluded that there is no evidence to support such a concept, chiefly because even totally paralyzed muscles undergo the same type of contracture as do other muscles.

OLIGODENDROGLIOMAS

A Review of Two Hundred Cases

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THE RECOGNITION of the oligodendrocyte as a cellular unit of the neuroglial portion of the central nervous system was made by Ford Robertson, a Scottish investigator, in 1900. With the use of platinum impregnation he separated a cell type from the third element of Cajal, which he called "mesoglia." Hortega, in 1918, analyzed the third element of Cajal with the use of silver carbonate impregnation methods and discovered first the microglial cell, which he called "microglia"; in 1921 he identified the oligodendroglial cell, which he so designated because of its few dendritic processes. The mesoglial cell of Robertson was found to correspond to the oligodendroglial cell of Hortega, but the term used by the latter was retained, since it was more descriptive and avoided implication of mesodermal derivation.

Bailey and Cushing,[1] in their historic classification of gliomas, published in 1926, were the first to associate the oligodendroglial cell with tumor formation. From observations made in a series of 9 cases, they segregated the oligodendroglioma from the glioma group and made the following descriptive notations:

> A cellular tumor of peculiar type, in which fibrillar astrocytes occasionally appear is sometimes encountered. The neoplastic cells have spherical nuclei with a heavy chromatinic network, and are surrounded by a ring of cytoplasm which stains very feebly by ordinary staining methods. Between the cells is an indefinite material which stains neither for neurofibrillae, neuroglia, nor for connective tissue.

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Abridgment of thesis submitted by Dr. Earnest to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Neurosurgery.

1. Bailey, P., and Cushing, H.: A Classification of the Tumors of the Glioma Group on a Histogenetic Basis, with a Correlated Study of Prognosis, Philadelphia, J. B. Lippincott Company, 1926.

This material may give the growth somewhat the appearance of the cross section of a plant. No mitotic figures can be seen. These tumors are prone to become calcified.

In their series the tumor was located always in the cerebrum, involving the frontal lobe most frequently, and originated usually as a subcortical lesion of a solid nature. The youngest patient was aged 5 years on admission, and the oldest, 48, the average age being 29.

To this initial description few noteworthy contributions have been made. Subsequent publications have served mainly to verify the tumor entity and further to refine the descriptive anatomy. The rather extreme controversial discussions are no doubt due to the sparsity of material for study, for most conclusions have been drawn from series of 2 to 13 cases, Cushing's series of 27 cases exceeding the others.

Bailey and Bucy,[2] in 1929, reported a study of 13 cases and more clearly defined the cytologic features of the tumor. They pointed out the rarity of mitotic figures, the moderate vascularity, the frequent increase in perivascular connective tissue, the common occurrence of endothelial proliferation and the presence of necrotic areas, astrocytes and spongioblasts. They stated that they could observe all stages of transition from the oligodendrocyte to the astrocyte. From the clinical standpoint, they observed that the tumor occurred most frequently in adults and affected predominantly the cerebral hemispheres, that the sexes were about equally affected and that the tumor was slow growing, causing symptoms for an average of 57.5 months before surgical treatment, with a postoperative survival period of more than 39.2 months, the average total survival period being 96.7 months. They stated that the calcium shadow seen in the roentgenogram was not diagnostic of the tumor type.

Kwan and Alpers,[3] in a classic article published in 1931, on the basis of a study of 4 cases, confirmed almost without exception the features emphasized by Bailey and Cushing[1] and Bailey and Bucy.[2] They pointed out the invasive nature of the tumor but noted in some cases a tendency to pseudocapsule formation or to a line of demarcation formed by fibrous tissue and neuroglial fibrils. They attributed this phenomenon to the slow growth of the neoplasm and the opportunity thus afforded the brain to develop a protective wall. They noted no calcium in any of the 4 cases.

One of us (J. W. K.[4]), in discussing the cytologic characteristics of 2 oligodendrogliomas of the spinal cord, entered the controversy con-

2. Bailey, P., and Bucy, P. C.: Oligodendrogliomas of the Brain, J. Path. & Bact. **32**:735-751, 1929.

3. Kwan, S. T., and Alpers, B. J.: The Oligodendrogliomas, Arch. Neurol. & Psychiat. **26**:279-321 (Aug.) 1931.

4. Kernohan, J. W.: Primary Tumors of the Spinal Cord and Intradural Filum Terminale, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 3, pp. 993-1025.

cerning the histogenesis by implying a relationship to the ependymal cell after noting atypical areas in the tumor structure in which the histologic picture more clearly resembled that of ependymoma than of oligodendroglioma. At the same time, an attempt was made further to refine the oligodendroglioma group by suggesting the possibility of an oligodendroblastoma group. It was noted that the 2 tumors reported on were composed in part of fairly well differentiated oligodendroglial cells and in part of more rapidly growing oligodendroglial cells, or, as one might call them, oligodendroblasts. Thus, the oligodendroblastoma, so named, was found to contain cells in which the nuclei were larger than those seen in an oligodendroglioma and the cytoplasm was visible. Binucleated cells were less abundant. Mitotic figures were present.

Cushing,[5] in 1932, reported the largest aggregate of cases for study in the English literature, a total of 27. Nine of these were from the original series of Bailey and Cushing, published in 1926. The unsettled status of the oligodendroglioma in the classification of tumors was once more made apparent by Cushing's interesting comments on a possible relation to the medulloblastoma. Cushing's statistics, for a period up to July 1931, revealed an occurrence of 27 oligodendrogliomas in a series of 2,023 tumors of the brain, 862 of which were gliomas. For 26 of the 27 patients a total of 46 operations were performed, with 4 postoperative fatalities. He reported a case mortality rate of 15.4 per cent and an operative mortality rate of 8.7 per cent.

Elvidge, Penfield and Cone[6] reported 8 cases of oligodendrogliomas of the central nervous system, which they divided into gliomas and blastomas. Only 1 in the series was a well differentiated oligodendroglioma, the remainder falling into the category of blastoma. Calcium deposits were present in at least 2 of the 8 cases. In all 8 cases mitotic figures were observed. Small cysts were present in 2 cases.

One of us (J. W. K.[7]) proposed a new classification of the gliomas based on a revised concept of histogenesis and cell relationships, calling attention once more to an apparent relationship between ependymal cells and oligodendrocytes and expressing the opinion once again that tumors of this type may properly be classified as oligodendrocytomas or oligodendroblastomas. The nucleus of the oligodendroblastoma was observed to be larger than that of the oligodendroglioma; some cytoplasm could be seen around the nucleus, and mitotic figures were commoner. A

5. Cushing, H.: Intracranial Tumors, Springfield, Ill., Charles C Thomas, Publisher, 1932, p. 49.

6. Elvidge, A.; Penfield, W., and Cone, W.: The Gliomas of the Central Nervous System, A. Research Nerv. & Ment. Dis., Proc. **16**:107-181, 1935.

7. Kernohan, J. W.: Tumors of the Central Nervous System, Proc. Staff Meet., Mayo Clin. **13**:827-832 (Dec. 28) 1938.

close association was noted between the oligodendroglioma or oligodendroblastoma and the ependymoma, particularly the cellular type.

The second largest series of oligodendrogliomas was reported by Shenkin, Grant and Drew [8] in December 1947. In their analysis of 25 cases, they called attention to the frequent relation to one of the ventricles (10 of 25 cases) and the predominant localization in the frontal lobe (16 of 25 cases). The lesions in 13 of the 25 cases were sufficiently calcified to be recognized roentgenologically. In 5 additional cases the lesions were found to contain calcium on microscopic examination. In comparing the clinical data with the microscopic picture, they made the following noteworthy statements:

> In no instances were there sufficient mitoses or other evidences of rapid growth which could be correlated with the clinical course of the patient to justify the formation of cases of the oligodendroblastomatous type. It was not possible, therefore, from the histologic appearance of the tumor to segregate a group in which the prognosis could be said to be more favorable.

MAYO CLINIC SERIES

This report on the Mayo Clinic series of oligodendrogliomas covers a period of thirty years (1918 through 1947). It is difficult, therefore, to draw final conclusions concerning such factors as the life history of the tumor, period of survival, mortality rate and deposition of calcium, for during this period many changes have occurred. A better understanding of neurophysiology, together with the introduction of chemotherapy and the use of antibiotics, has aided in the handling of patients with brain tumors; new instruments and technics have been of assistance to the neurosurgeon; roentgenologic technics and x-ray films have been greatly improved, and, finally, present day surgical neuropathology itself had its birth and development during this period. There is no common standard, therefore, by which we may safely measure our statistical data. However, with these difficulties in mind, we have attempted a review of the cases.

Breakdown of Cases.—Two hundred cases were considered in this study. Thirty-five cases were eliminated from the analysis because there was doubt concerning their precise identity or because sufficient tissue was not at hand to permit an adequate examination. A series of 165 cases of tumors of certain oligodendroglial derivation remained. Most of these cases fell into the surgical group. There were 46 hospital deaths. One hundred and twelve patients left the hospital, 5 of whom were never heard from.

8. Shenkin, H. A.; Grant, F. C., and Drew, J. H.: Postoperative Period of Survival of Patients with Oligodendroglioma of the Brain, Arch. Neurol. & Psychiat. **58**:710-715 (Dec.) 1947.

Various procedures were carried out in the surgical group. Thus, in 45 cases it was the opinion of the surgeon that the tumor was completely removed; in 62 cases partial removal was undertaken, and in 40 cases biopsy tissue only was taken from the tumor. Aspiration of cysts was carried out in 2 cases, and a ventriculogram only was made in 3 cases. In 6 cases exploration and decompression only were performed. Exclusive of patients who died while in the hospital and those who had not been heard from since they left the hospital, a series of 107 patients, referred to as "last reported," remained, composed of patients who died after leaving the hospital, as well as those still living.

Sex Distribution.—There seemed to be no significant sex predilection. Ninety-five of the patients were men and 70 were women.

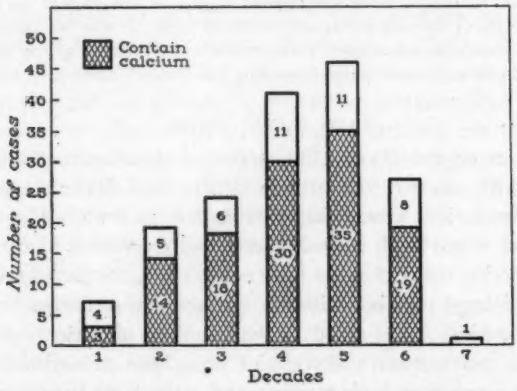

Fig. 1.—Age distribution of 165 patients with oligodendroglioma.

Age Distribution.—A review of the age distribution showed clearly that, although the tumor occurred most frequently in the fourth and fifth decades of life, it spared no age group and was surprisingly frequent at both extremes of life (youngest patient, 4 years; oldest patient 63 years). The average age was 36.25 years (fig. 1).

Site of Tumor.—The tumor affected predominantly the cerebral hemispheres, although nearly every part of the brain was implicated. In 151 of the cases it was supratentorial, and in 14 it was infratentorial. The frontal lobe was definitely the site of predilection. In 52 cases the tumor was located in this portion of the cerebrum, and in 27 others, in the frontal lobe in association with adjacent parts of the brain, making a total of 79 cases in which the tumor involved the frontal lobe. One hundred and forty-one of the supratentorial lesions involved the cerebral hemispheres. For 10 other tumors the location was the third ventricle, thalamus, lateral ventricle or region of the optic chiasm. Of the infra-

tentorial tumors, 5 were located in the vermis, 4 in the fourth ventricle, 3 in the cerebellum and 2 in the cerebellopontile angle. Of the entire group, 80 were on the left, 67 on the right and 13 in the midline, and 5 were bilateral. Five tumors involved the corpus callosum in their bilaterality; 32 bore some relation to a ventricle, and 35 were mentioned in the surgical notes as being subcortical.

By virtue of the large number of cases to be considered, perhaps the most reliable method of gaging the life span of the tumor was to be found in analysis of the cases in which operation was performed. It should be stated at the outset that the calculations derived by this method could not but be a gross underestimate of the true survival period of the patients considered, for, as the statistics indicate, the life span of the tumor is notoriously long. Since our series covered the period through 1947, the majority of the patients who were still living had in no sense approxi-

Statistics on Survival of the Surgical Patients

Postoperative Survival Period, Yr.	Biopsy Only *			Partial Removal *			Complete Removal *			Total *		
	L	D	T	L	D	T	L	D	T	L	D	T
Less than 1	4	4	8	2	5	7	2	10	12	8	19	27
1-4	..	12	12	5	20	25	9	9	18	14	41	55
5-9	..	4	4	1	3	4	5	1	6	6	8	14
10-14	..	1	1	1	1	2	1	..	1	2	2	4
15-19	1	..	1	..	..	..	..	1	1	1	1	2
20 or more	..	1	1	1	1	2	..	1	1	1	3	4
	5	22	27	10	30	40	17	22	39	32	74	106†
Average survival period, mo		49.5			51.0			44.5			48	

* L indicates that the patients were living, and D, that they had died; T designates the total number of patients.

† The contents of a cyst were aspirated in 1 patient who survived sixteen months, making the total number followed 107.

mated their probable life span. Furthermore, in spite of follow-up letters, we had no recent information on many of the patients known to have lived many months. So our figures, at best, measured the minimal limit of the life span of the tumor, and each successive year should extend this limit considerably.

From this study, the cases of patients who died in the hospital and those who had not been heard from since leaving the hospital were excluded, leaving 107 surgical cases for consideration. In this group the average period from the time of operation to death or to the time when the patient was last heard from was forty-eight months. A more nearly complete and significant analysis of this group can be derived from examination of the table, in which the data for each factor are divided according to whether the patient was living or dead. It is clearly shown that for the majority of the living patients, which comprised almost a third of the group, the possible survival period had

not yet had opportunity to reach twenty years, and thus contribute significantly to the length of the survival period.

A cursory examination of the average survival statistics set forth in the table might lead one to the erroneous impression that better results may be expected when complete removal is not carried out, but on closer scrutiny it will be noted that far more patients were living after complete removal than after partial removal, thus producing substantial evidence in favor of the more radical procedure and indicating clearly that with time the average survival figure for this group will surely far exceed the others.

To complete the picture of the life span, we added to the survival period the period from the first symptom to the date of operation. One hundred and fifty-seven of the cases in which operation was performed permitted such an analysis, and in this group the average period was 43.5 months. This figure, when added to the average survival period of forty-eight months, gave a minimal estimate of the life span after appearance of the first symptoms of 91.5 months.

It is interesting to note that the longest preoperative period was 256 months. The longest postoperative survival was 316 months. The longest complete survival after appearance of the first symptom was 333 months (27.8 years), and the patient was still living at the time of writing.

From the data thus far submitted, it seems safe to estimate that the average life span of an oligodendroglioma is between eight and fourteen years, and may be much longer. The fact that the tumor may exist for a considerable period in a silent phase is rather feebly supported by a case in the nonsurgical group in which the tumor was discovered incidentally at necropsy. One is tempted to deduce from this that with the first symptom the tumor may be well established.

Deposition of Calcium.—Calcium was found in 115 cases (69.7 per cent). In 64 cases (38.8 per cent) this was noted on roentgenologic examination. The tumors in the additional 51 cases were found to contain calcium on microscopic examination. In figure 1 it is seen that deposition of calcium occurred with the same relative frequency in all age groups.

Gross and Microscopic Features.—There is ample description in the literature of the gross features of the tumor under consideration, and this description is in agreement with that derived from the operative notes in our series. In summary, it can be said that the tumor was most frequently a pinkish red, friable mass, varying in size, with a rather deceptive pseudoplane of demarcation from the brain. Calcium was frequently detected grossly. In our series, 32 tumors were cystic. This no doubt is an underestimate, for in the cases in which biopsy was performed and in certain others the cystic nature could not be ascertained.

In 35 instances the operative note described the lesion as subcortical. Of the tumors reaching the surface of the cortex, the presenting portion frequently spread out in mushroom fashion.

For study of the microscopic features of the tumor, the hematoxylin and eosin technic of staining was used. In a review of the series, it was soon apparent that, although the so-called typical basic monotonous pattern of small round nuclei with halo formation prevailed, there was a wide range of cytologic variation. The nuclei were not always round; they were not always placed in a halo-like space; the cells were not always of uniform size; there was variability in staining reaction, and in some areas the cytoplasm stained a pale pink. Mitotic figures were seen often. Endothelial proliferation was observed frequently, with considerable variation in the vascularity of the tumors. Areas of necrosis were not uncommon. Calcium was deposited in the parenchyma of the tumor, and in many instances in or around blood vessels. The tumor was seen to be definitely infiltrative with a rather wide zone of transition between the tumor proper and the parenchyma of the brain, and the tumor was, nearly without exception, much more extensive than the neurologic picture would indicate. In fact, it would seem that the parts of the brain involved must function longer after they have been invaded by tumor tissue.

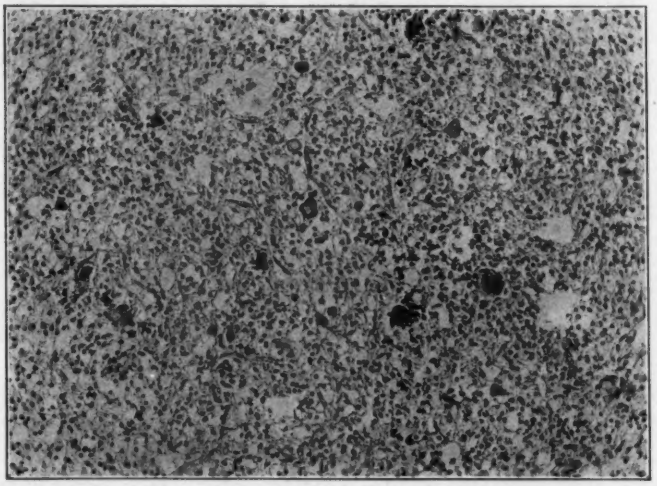

Fig. 2.—Appearance of a typical oligodendroglioma. Hematoxylin and eosin; × 100.

The tumors of oligodendroglial derivation were divided into two groups on the basis of their general architecture and cellular constituents.

The first group consists of the oligodendrogliomas, which are tumors of the mature, adult type of oligocytes assembled so that with the hematoxylin and eosin stain the tissue has a honeycomb appearance. Deposition of calcium is not essential to the picture. Mitotic figures may be seen (fig. 2).

Oligodendroblastomas comprise the second group, and the term is intended to have the same connotation here as that previously suggested. The tumor contains areas in addition to, or in place of, those already described, in which the cellular constituents show some variability. The nuclei are frequently large, often oval, and the cytoplasm

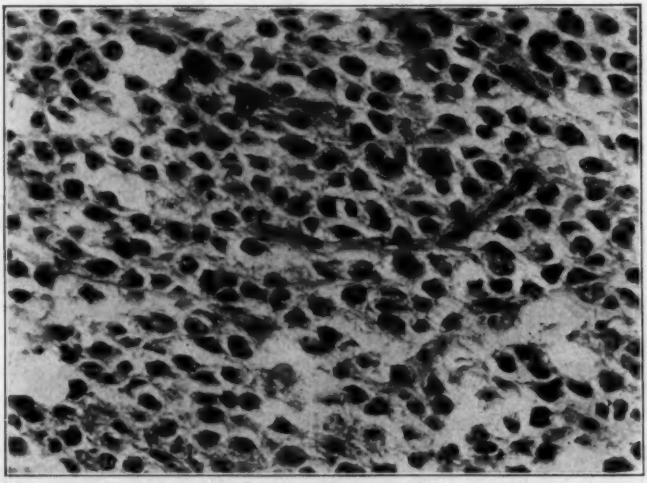

Fig. 3.—Oligodendroblastoma, showing pleomorphism and many mitotic figures. Hematoxylin and eosin; × 285.

stains pink. A certain monotony of the cytologic picture persists in spite of these changes, but the true honeycomb appearance is distorted to varying degrees. Calcium may or may not be present. Mitotic figures are seen. Vascular reactions in the form of proliferation of the endothelium are more frequently identified in oligodendroblastomas but may be present also in oligodendrogliomas (fig. 3).

Sixty-eight tumors were classified as oligodendrogliomas and 97, as oligodendroblastomas.

An interesting development of the microscopic study appeared in consideration of the relation of these tumors to those of the ependymoma group. Frequently, the tumor lost its honeycomb appearance, and the cells were seen lining up and following the course of a fine net-

work of blood vessels, often forming papillary-like arrangements and pseudorosettes. The cells themselves often retained their oligodendroglial identity, but in many instances the nuclei appeared larger, were oblong or oval and contained less chromatin, and the cytoplasm stained pink, giving the cell an ependyma-like appearance. The typical appearance of oligodendroglioma and of oligodendroglioma with ependyma-like cells is shown in *a* and *b*, respectively, of figure 4. Some suggestion of ependymal relation, either in general architecture or in cellular detail,

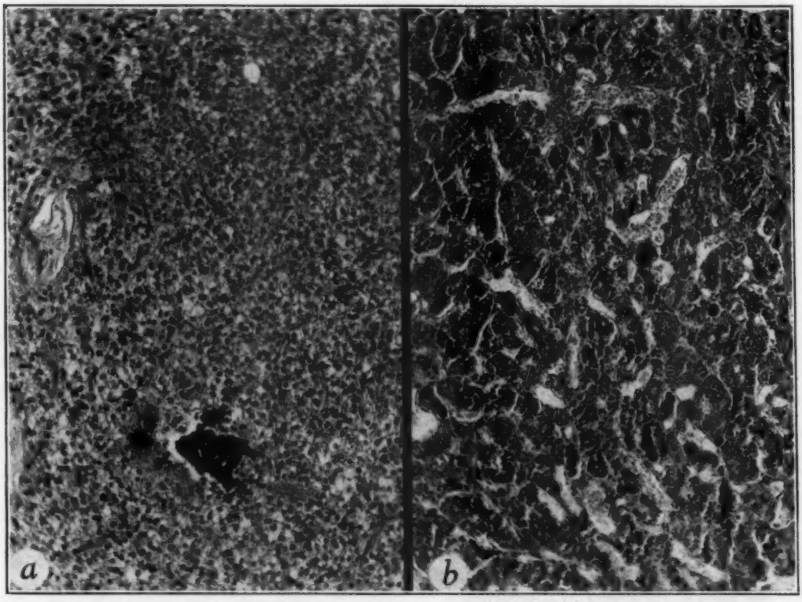

Fig. 4.—(*a*), Mature-looking oligodendroglioma; (*b*), area with ependymoma-like appearance from same tumor as that shown in *a*. Hematoxylin and eosin; × 100.

was noted in 48 cases, a resemblance tending to support materially the previously cited observation that there is some relationship between the ependymoma and the oligodendroglioma.

The contention that the oligodendroglial cells represent a transitional type of astrocyte could not be supported by the results of our study. Astrocytes were seen, but not in significantly large numbers to seem important from this standpoint. The frequency with which an oligodendroglioma is related to the ventricular system seems to be further borne out by the fact that seeding of the tumor via the cerebrospinal fluid was

noted in 14 cases (fig. 5). The spinal cord was implicated in this process in 3 cases.

Grading.—In February 1949, Svien and co-workers [9] and Mabon and co-workers,[10] in collaboration, proposed a system of grading of tumors of the glioma group on the basis of their malignancy, similar to that developed by Broders for tumors involving other tissues of the body. Thus, by an arbitrary division into four grades, the malignancy of the tumor could be conveniently catalogued from 1 to 4, and an estimate of the life cycle of the tumor, with its implication of survival for the patient, could be readily made. Such a system was successfully applied by them to the astrocytoma and ependymoma groups. The

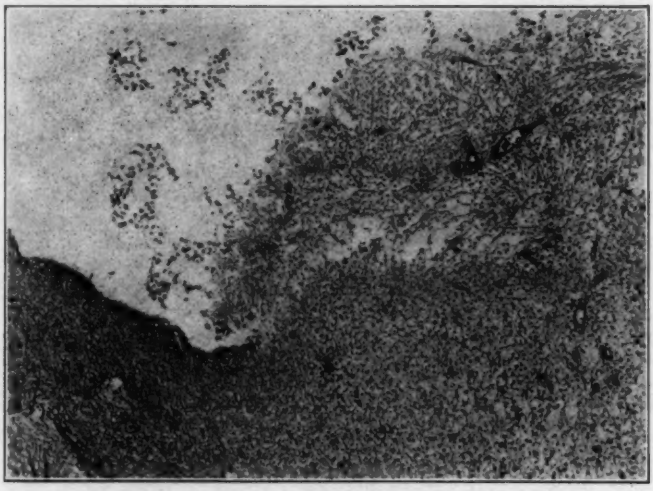

Fig. 5.—An area in which oligodendroglial cells have been seeded adjacent to the normal ependyma of a ventricle.

criteria for the various grades of malignancy in the astrocytoma group were summarized as follows: Grade 1 is characterized by normal-appearing astrocytes with no anaplasia. Grade 2 is characterized by early anaplastic transformation of some, or a small number, of the cells. No mitotic figures are present. Grade 3 is characterized by moderate anaplastic transformation of many more cells. Mitotic figures are present, averaging one for every other high power field. Grade 4 is characterized by marked anaplastic transformation of most cells. Mitotic

9. Svien, H. J.; Mabon, R. F.; Kernohan, J. W., and Adson, A. W.: Astrocytomas, Proc. Staff Meet., Mayo Clin. **24**:54-64 (Feb. 2) 1949.

10. Mabon, R. F.; Svien, H. J.; Kernohan, J. W., and Craig, W. McK.: Ependymomas, Proc. Staff Meet., Mayo Clin. **24**:65-71 (Feb. 2) 1949.

figures are abundant, averaging four or five per high power field. The criteria for the grading of tumors of the ependymoma group were similar.

The oligodendroglioma is an important tumor of the glioma group to which this system has not been applied. The comparatively large number of such tumors in the Mayo Clinic series of brain neoplasms has afforded an excellent opportunity for selectivity and has permitted the reduction to a minimum of certain obvious hazards in such an analysis.

When one is measuring malignancy against the survival time, certain facts should be kept in mind. The life history of the tumor may be altered by factors completely foreign to the histologic picture. The tumor may choose to grow in a so-called silent part of the brain or in a very vulnerable region, altering the sequence of events considerably. As an illustration of these extremes, the tumor in 1 case was discovered at necropsy, and its presence was quite incidental to the illness that caused the patient's death. On the other hand, a much smaller lesion in the midline may produce a violent neurologic picture in a relatively short time, leading promptly to death. Both tumors may be histologically benign.

To minimize this feature, the frontal lobe was selected as the laboratory for the study of the growth of this neoplasm, for thus variations in histologic appearance could more justifiably be related to variations in malignancy. The frontal lobe is particularly serviceable, since operation carried out in this region alters the dynamic factors—whatever they are —to the least degree, thus allowing one to continue the observation of the tumor through the postoperative phase.

In order further to minimize to the greatest degree the factors which might direct us to erroneous concepts, we thought it wise in this investigation of tumor cytology to exclude the data obtained from biopsies. To be sure, the grading of tumors finds its most important application to the examination of biopsy specimens for the neurosurgeon's operative guidance, but the groundwork for the grading seemed necessarily to be constructed from the group of cases in which sufficient tumor tissue was removed to permit an adequate survey of the cytologic characteristics.

Having reduced the obvious factors of error to a minimum, we attacked the problem of grading by two methods. First, the cytologic characteristics of the tumors in the series were studied, and the cases were arranged on a tentative basis of malignancy. The data so obtained were then applied to the clinical material as a test of validity. Second, the clinical data were examined, and the tumors were classified according to tentative degrees of malignancy on the basis of the life history of the tumor. The cytologic characteristics of the constituents of the

arbitrary groups were then examined in an effort to note tendencies toward unification of the cytologic features.

A satisfactory system of grading could not be devised by either method of approach. Apparently, mitotic figures do not carry the same significance in the oligodendroglial tumors as they do in other groups. Tumors that appeared benign frequently contained them. In several instances patients with a tumor displaying considerable pleomorphism and anaplasia survived many years, whereas paradoxically, many patients with so-called mature and benign oligodendrogliomas died early in the postoperative phase. Furthermore, the appearance of calcium had no apparent bearing on the malignancy of the tumor, for deposits were noted with similar frequency in all the tentative categories.

The classification of the tumors as oligodendrogliomas and oligodendroblastomas on the basis of microscopic examination seems to lose significance when applied to survival periods. In the series of patients selected for the study of grading, 20 members of the oligodendroglioma group had a survival period of 48.8 months, and 26 members of the oligodendroblastoma group had a survival period of 44.3 months. As a general rule, however, it is probably safe to anticipate a longer period of survival for the patients with oligodendroglial tumors.

SUMMARY

From this study of 200 cases of oligodendroglioma, certain features tending to define this tumor entity were outstanding. The growth appeared to be one primarily of the fourth and fifth decades and affected the sexes about equally. It was most commonly located in the cerebral hemispheres as a subcortical infiltrating neoplasm, but in rare instances practically any other part of the brain was involved. The life span of the tumor was long, being estimated as from eight to fourteen years. Deposition of calcium was a rather characteristic phenomenon of this tumor, regardless of the age of the patient or the location of the tumor, and appeared relatively early in the development of the neoplasm, probably between the second and the third year of growth. Histologically, the tumors could be conveniently classified as oligodendrogliomas and oligodendroblastomas. Certain histologic variations in general pattern and cellular detail were substantial evidence of a relation to the ependymoma. These tumors did not lend themselves well to grading with respect to degree of malignancy. Perhaps the criteria established for the grading of tumors are not applicable to oligodendrogliomas. It is logical to assume that the factors which influence the rapidity of growth should be reflected in the histologic picture. Possibly future studies will disclose these features, or perhaps a revision of present day precepts will prove peculiarly applicable to this tumor entity.

News and Comment

INTERNATIONAL CONGRESS OF PSYCHIATRY

The International Congress of Psychiatry (at present representing forty-one countries), will be held in Paris from Sept. 18 to 27, 1950. The program follows.

I. Scientific Program.—A. Six main topics will be discussed in the afternoon sessions.

SECTION 1: *Psychopathology of Delusions*
Chairman: Ferdinand Morel, Geneva
Speakers: P. Guiraud, Paris; W. Mayer-Gross, Dumfries, Scotland; E. Morselli, Novara, Italy; H. C. Rumke, Utrecht, Netherlands

SECTION 2: *Application of Mental Tests to Clinical Psychiatry*
Chairman: Honorio Delgado, Lima, Peru
Speakers: M. Bleuler, Zurich; Alfredo Guera, Madrid; R. Nyssen, Brussels; P. Pichot, Paris; David Rappaport, Stockbridge, Mass.

SECTION 3: *Cerebral Anatomy and Physiology in the Light of Lobotomies and Lobectomies*
Chairman: Frederick L. Golla, London
Speakers: H. J. de Barahona Fernandes, Lisbon; Walter Freeman, Washington, D. C.; Alfred Meyer, London

SECTION 4: *Indications for the Shock Therapy Methods*
Chairman: Josef Handelsman, Warsaw
Speakers: U. Cerletti, Rome; Rysrard Dreszer, Poznań; M. Fiamberti, Varesse, Italy; Juan Lopez Ibor, Madrid; L. Meduna, Chicago; Manfred Sakel, New York

SECTION 5: *Evolution and Present Trends of Psychoanalysis*
Chairman: Franz Alexander, Chicago
Speakers: Franz Alexander, Chicago; Anna Freud, London; Maurice Levine, Cincinnati; Raymond de Saussure, New York

SECTION 6: *Genetics and Eugenics*
Chairman: Torsten Sjögren, Stockholm
Speakers: Franz Kallmann, New York; Lionel Penrose, London; J. A. Fraser-Roberts, London; Eliot Slater, London; Erik Strömgren, Risskov

SECTION 7: *Behavior Problems in Childhood and Their Prognoses* (no report)

All the reports for the main plenary sessions are already printed, in six volumes, which will be sent to the registered members and to the psychiatric societies of each country, to be discussed before the final sessions, in Paris.

B. Five mornings will be devoted to debates (important meetings of discussion, with speakers and reports).

SECTION 1
Psychopathology of Depersonalization
Notions of Evolution and Disintegration of the Psychic Functions in Psychopathology

SECTION 2
Clinical Subdivision of the Schizophrenia Group
Clinical Study of the Atrophic Dementias

SECTION 3
Electroencephalography in Psychiatry
Experimental Catatonias

SECTION 4
Therapeutic Aspects of the Lobotomies
Endocrinal Therapies

SECTION 5
Group Psychotherapy
Psychogenesis of the Somatic Manifestations

SECTION 6
War Events and Mental Disorders
Problem of Progression of Mental Disorders in Modern Society

A special meeting is reserved for further discussion on the subjects of the plenary sessions.

C. Symposiums (small meetings of an intimate nature) will be held on the following subjects:

SECTION 1
Psychopathology of Auditory and Visual Hallucinations
Existential Analysis
Experimental Neuroses by Conditioning
Constitutional Typology

SECTION 2
Narcoanalysis
Prognosis of the Puerperal Psychoses
Psychopathic Personalities
Final Stages of Manic-Depressive Psychoses
Statistical Classification of Mental Diseases of the World Health Organization

SECTION 3
Maturation of the Nervous System
Biochemical Factors Affecting Ability to Form Conditioned Reflexes
Dysmetabolic Oligophrenias
Cerebrospinal Fluid in Psychiatry
Isotopes in Psychiatry
Cybernetics: Cerebral and Psychic Functions
Pneumoencephalography
Cerebral Chemistry

SECTION 4
Electronarcosis
Therapy of Alcoholism
Sleep Treatment
Vitamins in Therapeutic Psychiatry

SECTION 5
Psychosomatic Medicine of the Stomach: Gastritis and Ulcers
Psychotherapy of Schizophrenia
Psychoanalysis and Daydreaming
Possibilities of Psychotherapy and Psychoanalysis in Hospital Spheres
Hypnotherapy

SECTION 6

Architecture of Psychiatric Institutions
Disablement and Incapacity for Working Conditioned by Mental Disorders
Special Services for Delinquents
Comparative Legislations and Relief Organizations in the Various Countries
What is Meant by Social Psychiatry?

The plenary sessions will be held at the Sorbonne, and during these sessions "simultaneous interpretation" will be available. In the morning debates, a system of "consecutive interpretation," in English and in French only, will be set up.

II Exhibitions.—An exhibition of psychopathologic art will be held at the Psychiatric Center of Sainte Anne.

An exhibition on the history and progress of psychiatry (president, Prof. Laignel-Lavastine) will be held at the Palais de la Découverte.

Finally, in the Hall of the Sorbonne, there will be an exhibition of psychiatric books and magazines.

III. Receptions; Trips; Entertainments.—An important program of receptions and entertainments is being set up: concerts, theatrical performances, evening receptions at the Palais de Chaillot, the Louvre, etc. Besides, there will be visits to psychiatric centers and trips across the country surrounding Paris.

The fee for registered members is 6,000 francs and for associate members (family) 3,000 francs. The International Congress of Psychiatry is reserved to physicians; eventually, psychologists, psychoanalysts and biologists will be welcome.

At the International Meeting of Oct. 24, 1947, the organizing committee of the International Congress of Psychiatry was appointed: honorary chairmen, Prof. P. Janet (in memoriam) and Prof. Jean Lhermitte; chairman, Prof. J. Delay; general secretary, Dr. Henri Ey; treasurer, Dr. P. Sivadon.

Correspondence may be directed to Congrès International de Psychiatrie, 1, rue Cabanis, Paris XIV°.

NOTICE

The index for Volume 63 will be mailed with the July 1950 number.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

INFLUENCE OF THE PERIPHERAL FIELD ON THE DEVELOPMENT OF THE MESENCEPHALIC V NUCLEUS IN AMBLYSTOMA. JEAN PIATT, J. Exper. Zool. **102**:109 (June) 1946.

Experiments were designed to test the effect of hyperplasia or hypoplasia of a specific peripheral field (levator mandibulae muscles) on its afferent, intramedullary neurons (mesencephalic nucleus of the fifth cranial nerve) in the urodele. Experiments in which the jaw muscle field was completely abolished or greatly reduced (removal of right mandibular arch at stages 27 to 29) showed a consistent reduction of 41.2 per cent in the number of cells of the mesencephalic fifth root cells in the optic tectum on the side of operation. However, there was no pronounced hypoplasia in the more caudal cells of this nucleus (anterior medullary velum and nucleus posterior tecti) on either the same or the opposite side.

Experiments in which the jaw muscle field was greatly increased by substitution of the right mandibular arch of Amblystoma tigrinum (donor) for that of Amblystoma punctatum (host) at stages 30 to 32 showed a small but consistent increase (16.6 per cent) in the number of cells of the mesencephalic fifth root in the optic tectum on the side of operation. The cells lying in the caudal part of this nucleus exhibited no hyperplasia.

When the eye muscle volume was reduced (removal of the optic vesicle and adjacent mesoderm, unilateral or bilateral, at stage 30), there was no consistent or significant reduction in the number of cells of the mesencephalic fifth root on either side. This result applied to the entire nucleus, but the series (5 cases) is considered too few for a proper evaluation of the results.

Since these experiments have demonstrated that either an increase or a decrease in the peripheral field exerts a specific regulatory effect on the intramedullary cells of the mesencephalic fifth nucleus of the optic tectum, it is concluded that the definitive details of the central nervous system of the salamander are subject to the same peripheral conditioning as that exhibited in other vertebrates.

The bearing which these experimental data have on the peripheral distribution of the mesencephalic fifth root is discussed; the optic tectum furnishes afferent fibers to the jaw muscles.

REID, New Brunswick, N. J.

Physiology and Biochemistry

CHOLINERGIC AND ADRENERGIC COMPONENTS IN THE NEUROHUMERAL CONTROL OF THE RELEASE OF LH IN THE RABBIT. C. H. SAWYER, J. E. MARKEE and B. F. TOWNSEND, Endocrinology **44**:18 (Jan.) 1949.

Sawyer, Markee and Townsend investigated the mechanism through which the central nervous system causes the anterior lobe of the hypophysis to release luteinizing hormone after copulation in animals which do not ovulate spontaneously. They have found that copulation-induced ovulation, signifying the release of luteinizing hormones, can be blocked by the administration of dibenamine (dibenzyl-beta-chlorethylamine), an adrenolytic agent, and by atropine. Atropine, to be equally effective, must be given earlier than dibenamine. Thus, a cholinergic,

atropine-blocked component of the copulation-initiated neurogenic stimulus appears to precede the adrenergic component. The authors conclude that the final pathway of the natural neurogenic stimulus at copulation is the hypophysial portal system, where the cholinergic component stimulates the secretion of the adrenergic mediator; the latter, in turn, stimulates the hypophysial cells to release luteinizing hormone.

FRANKEL, Philadelphia.

EFFECTS OF TESTOSTERONE PROPIONATE UPON SEXUAL LIBIDO AND THE PRODUCTION OF SEMEN AND SPERM IN THE RABBIT. PEILIEU CHENG and L. E. CASIDA, Endocrinology **44**:38 (Jan.) 1949.

Cheng and Casida studied the effect of parenterally administered testosterone propionate on testicular function in rabbits. Sexual activity was increased. The total volume of the semen remained constant and the total number of sperm cells was not definitely affected, but their motility was improved.

FRANKEL, Philadelphia.

INVESTIGATION OF THE α- AND β-PHOSPHOLIPIDES. C. F. BURMASTER, J. Biol. Chem. **165**:565, 1946.

The α- and β-lecithins and α- and β-cephalins, instead of being pure isomers, as reported in the literature, were found to contain approximately equal amounts of α- and β-glycerophosphate. The solubility differences observed are not due to isomerism of the glycerophosphates. The β-cephalin fraction of calf brain resembled closely in appearance and solubility the inositol phospholipid described by Folch and Woolley.

PAGE, Cleveland.

THE INHIBITION OF THE ANAEROBIC GLYCOLYSIS OF RAT BRAIN BY ADRENOCHROME. L. O. RANDALL, J. Biol. Chem. **165**:733, 1946.

The anaerobic glycolysis of rat brain homogenates has been found to be inhibited by small concentrations of adrenochrome. Adenosine triphosphate, which increases the rate of glycolysis, partially overcomes the inhibition due to adrenochrome. Glutathione, which has no effect on the glycolytic rate, abolishes the inhibitory effect of adrenochrome. Since oxidizing agents, such as iodine, quinone and dichlorophenolindophenol, produce an inhibition of glycolysis which is reversed by glutathione, it appears possible that adrenochrome also inhibits by a reversible oxidation of the sulfhydryl groups of the enzymes of glycolysis.

PAGE, Cleveland.

SPECTROPHOTOMETRIC MEASUREMENT OF HEXOKINASE AND PHOSPHOHEXOKINASE ACTIVITY. E. RACKER, J. Biol. Chem. **167**:843, 1947.

Hexokinase was first discovered by Meyerhof. Later, through the work of von Euler and Adler, Meyerhof and Colowick, and Kalckar, with the use of partially purified preparations, it was established that in the presence of hexokinase and magnesium ions the following reaction occurs:

Adenosine triphosphate + glucose → adenosine diphosphate + glucose-6-phosphate

Phosphohexokinase has been studied only in crude tissue extracts. In analogy with the hexokinase enzyme, the reaction catalyzed by phosphohexokinase has been written as follows:

Adenosine triphosphate + fructose-6-phosphate → adenosine diphosphate + fructose-1,6-diphosphate

The methods available for the quantitative assay of these enzymes are based on phosphate transfer determinations and on changes in p_H of the reaction mixture.

They require large quantities of adenosine triphosphate and, for estimation in crude tissue extracts, the addition of inhibitors, such as iodoacetate and sodium fluoride. The purpose of this paper is to report a simple and rapid spectrophotometric method by which the rates of phosphorylation by the enzymes hexokinase and phosphohexokinase can be measured. The method has been used to measure these enzymes in brain extracts.

PAGE, Cleveland.

FREE AMINO ACIDS IN CEREBROSPINAL FLUID. J. D. SOLOMON, S. W. HIER and O. BERGEIM, J. Biol. Chem. **171**:695, 1947.

A method for the microbiologic determination of free amino acids in the cerebrospinal fluid is described. Results are presented for eleven free amino acids in the spinal fluid of 26 subjects. Average values, expressed in micrograms per cubic centimeter, were as follows: arginine, 6.0 ± 1.4; histidine, 1.7 ± 0.5; isoleucine, 0.98 ± 0.5; leucine, 1.4 ± 0.2; lysine, 2.8 ± 0.8; phenylalanine, 1.9 ± 0.7; threonine, 2.8 ± 0.9; tyrosine, 2.0 ± 0.7; valine, 2.1 ± 0.5; methionine, 0.4 ± 0.09, and cystine, 1.8 ± 0.5. The values vary from about one-fourth to one-fifteenth those for blood plasma. No significant changes were noted in the free amino acids in the spinal fluids of epileptic patients. An analysis of spinal fluid protein is reported.

PAGE, Cleveland.

ISOLATION AND IDENTIFICATION OF HYDROLECITHIN (DIPALMITYL LECITHIN) FROM BRAIN AND SPLEEN. S. J. THANNHAUSER and N. F. BONCODDO, J. Biol. Chem. **172**:135, 1948.

A method of isolation of crystalline hydrolecithin from beef brain is described. The isolated saturated lecithin is dipalmityl lecithin and is identical with lung hydrolecithin. Hydrolecithin was also isolated from spleen according to the procedure applied for its isolation from lung. It is identical with dipalmityl lecithin prepared from brain and lung. The yield of hydrolecithin in brain is approximately 4 Gm. from 25 pounds (3.5 Gm. per 10 Kg.) of fresh beef brain, corresponding to 25 to 40 per cent of the yield of sphingomyelin.

PAGE, Cleveland.

CHEMICAL NATURE OF THE FATTY ACIDS OF BRAIN AND SPLEEN SPHINGOMYELIN: OCCURRENCE OF SATURATED AND UNSATURATED SPHINGOSINES IN THE SPHINGOMYELIN MOLECULE. S. J. THANNHAUSER and N. F. BONCODDO, J. Biol. Chem. **172**:141, 1948.

A procedure for the preparation of pure brain sphingomyelin, free of hydrolecithin, is described. The fatty acids present in the sphingomyelin of brain are different from those present in the sphingomyelin of other organs investigated. The component fatty acids of brain sphingomyelin are stearic, nervonic and lignoceric acids, while lignoceric acid and palmitic acid are the component fatty acids of sphingomyelin prepared from spleen and lung. Sphingosine isolated after acid hydrolysis of brain, as well as spleen sphingomyelin, is a mixture of hydrosphingosine and unsaturated sphingosine.

PAGE, Cleveland.

THE AMMONIA AND GLUTAMINE CONTENT OF THE BRAIN. D. RICHTER and R. M. C. DAWSON, J. Biol. Chem. **176**:1199, 1948.

The values given in the literature for the ammonia content of the brain show wide variation. Most of these values are of doubtful reliability, since the methods of estimation have not generally taken into account the presence of labile acid

amides, such as glutamine, which are now known to occur in the brain and which easily liberate ammonia on treatment with alkalis under the conditions commonly used for the estimation of ammonia. Values are reported by Richter and Dawson for the ammonia and glutamine contents of the rat brain. The normal ammonia content, determined by a method which avoided the error due to the decomposition of labile acid amides, was 0.28 mg., and the glutamine content 79 mg. per hundred cubic centimeters. A study of the factors affecting the ammonia level of the brain showed that the ammonia was decreased by prolonged pentobarbital narcosis and notably increased by direct stimulation of the brain or by procedures which increase cerebral irritability. The ammonia level was increased to 0.47 mg. per hundred cubic centimeters by administration of picrotoxin and 0.81 mg. per hundred cubic centimeters by anoxia. Electrical stimulation caused a rapid increase in the ammonia level in one to two seconds, and it was also raised by the stimulus of decapitation. The ammonia content of the brain was not affected by emotional excitement, and the glutamine content was not significantly altered by any of the factors which were tested. Injection of ammonium chloride in the rat caused convulsions when the ammonia level of the brain had risen to 9 mg. per hundred cubic centimeters. The significance of these data in relation to the mechanism of epileptic seizures is discussed.

PAGE, Cleveland.

COMPLETE FRACTIONATION OF BRAIN CEPHALIN: ISOLATION FROM IT OF PHOSPHATIDYL SERINE, PHOSPHATIDYL ETHANOLAMINE, AND DIPHOSPHOINOSITIDE. J. FOLCH, J. Biol. Chem. **177**:497, 1949.

Brain cephalin has been found to be a mixture of phosphatidyl serine, phosphatidyl ethanolamine and a new inositol-containing phosphatide, which is called diphosphoinositide.

PAGE, Cleveland.

BRAIN DIPHOSPHOINOSITIDE, A NEW PHOSPHATIDE HAVING INOSITOL METADIPHOSPHATE AS A CONSTITUENT. J. FOLCH, J. Biol. Chem. **177**:505, 1949.

Diphosphoinositide, a new brain phosphatide, has been seperated from brain cephalin. This phosphatide accounts for all the inositol present in brain cephalin. The constituents of the new phosphatide appear to be inositol metadiphosphate, glycerol and fatty acids, in equimolar proportions. Inositol metadiphosphate, which has been isolated, among the products of short time acid hydrolysis of diphosphoinositide, has been identified by its elementary composition, by titration with alkali, by isolation from it of inositol and by the study of the products of its reaction with periodic acid (HIO_4). On reacting with periodic acid, each mole of inositol diphosphate has been found to use 2 moles of periodic acid and to produce 1 mole of formic acid. This is consistent with a meta position of the two phosphoryl radicals on the inositol molecule. Besides the constituents enumerated, diphosphoinositide contains as contaminants carbohydrate-containing lipids. Nitrogen present in diphosphoinositide preparations also appears to be a contaminant.

PAGE, Cleveland.

THE NITROGENOUS CONSTITUENTS OF THE TISSUE LIPIDES: II. THE DETERMINATION OF SPHINGOSINE IN TISSUE LIPIDE EXTRACTS. J. M. MCKIBBIN and W. E. TAYLOR, J. Biol. Chem. **178**:29, 1949.

A method is described for an approximate determination of sphingosine in whole lipid extracts which have been freed of nonlipid impurities. The method is based

on a chloroform extraction of the aqueous lipid hydrolysate which is both specific and relatively quantitative for sphingosine. Sphingosine is then determined on the chloroform extract as nitrogen. The method has been used routinely in the range of 6 to 20 millimoles of sphingosine with triplicate nitrogen analyses. Sphingosine nitrogen comprised from 8 to 35 per cent of total lipid nitrogen in the tissues analyzed.

PAGE, Cleveland.

BIOCHEMICAL STUDIES ON DIPHENHYDRAMINE (BENADRYL®): II. DISTRIBUTION IN TISSUES AND URINARY EXCRETION. A. J. GLAZKO and W. A. DILL, J. Biol. Chem. **179**:403, 1949.

Comparative data are presented on the levels of diphenhydramine (benadryl®) in rat and guinea pig tissues at different intervals after administration of the drug. After subcutaneous injection the highest concentrations were found in the lungs, with progressively lower concentrations in the spleen, kidney, brain, liver and muscle. Peak concentrations were found in about one hour, with a fairly rapid drop toward a normal level in six hours. The presence of a small amount of unaltered diphenhydramine was demonstrated in human urine by means of countercurrent solvent extraction and ultraviolet ray absorption characteristics.

PAGE, Cleveland.

BIOCHEMICAL STUDIES ON DIPHENHYDRAMINE (BENADRYL): IV. DEGRADATION OF BENADRYL BY TISSUE ENZYMES. A. J. GLAZKO and W. A. DILL, J. Biol. Chem. **179**:417, 1949.

The basic properties of diphenhydramine (benadryl®) are lost through the action of a tissue enzyme system which is partly characterized. The liver appears to be the best source of this enzyme, with some activity observed in lung and kidney tissue. The reaction appears to be monomolecular, with the optimum p_H in the physiologic range. Oxygen is required for the reaction, and various reducing agents are shown to act as inhibitors. Minced liver, lung and kidney degrade diphenhydramine much more actively than brain, heart, spleen and muscle.

PAGE, Cleveland.

CHOLINERGIC STIMULATION OF THE RELEASE OF MELANOPHORE HORMONE BY THE HYPOPHYSIS IN SALAMANDER LARVAE. CHARLES H. SAWYER, J. Exper. Zool. **106**:145 (Nov.) 1947.

Sawyer reports the effect of cholinergic drugs on pigment dispersion during the primary, or nonvisual, phase of melanophore activity in salamander larvae (Amblystoma punctatum and Triturus torosus).

In general, cholinergic drugs induce melanophore expansion by a direct action on the pigment cells in the prepituitary stage, but by the mediation of the melanophore hormone of the hypophysis in the later developmental (pituitary) stage.

In low concentration atropine inhibits natural melanophore expansion during early or later stages and prevents acetylcholine-induced darkening during the prepituitary phase. However, in low concentration atropine fails to inhibit pigment dispersion stimulated by physostigmine or neostigmine. In higher concentration atropine causes melanophore expansion in both intact and hypophysectomized larvae. Melanophore activity is not affected by nicotine.

In the nonvisual phase epinephrine induces pigment dispersion by a direct effect on the melanophores. Epinephrine also produces vasodilation of the gill capillaries,

whereas acetylcholine or physostigmine causes vasoconstriction and atrophy of the gills.

In the pituitary stage physostigmine alone retains a slight direct effect on the pigment cells, for all other cholinergic drugs fail to induce melanophore expansion in hypophysectomized larvae. When melanophore hormone and physostigmine or neostigmine were supplied extrinsically to hypophysectomized animals, there was no synergism between drug and hormone. Sawyer concludes that cholinergic drugs induce melanophore expansion during the pituitary stage by stimulating the secretion of the melanophore hormone by the hypophysis.

REID, New Brunswick, N. J.

DISTRIBUTION OF COPPER ^{64} IN EARLY EMBRYO CHICKS. ELLEN E. SMITH and PETER GRAY, J. Exper. Zool. **107**:183 (March) 1948.

About 200 eggs of S.C. white leghorn hens were injected with radioactive copper ^{64} after zero, twenty-four and forty-eight hours of incubation, and the resulting embryos were removed twenty-four to forty-eight hours later, when autoradiograms were made. The clearest autoradiograms, which covered the period from fifteen to eighty-four hours of incubation, were used for the study.

Copper ^{64} tended to be distributed in certain patterns: (*a*) A primary anteroposteriad gradient from the 4 somite stage through the 78 hour stage. This gradient began to develop in the head fold stage and disappeared at the 78 hour stage. (*b*) A secondary posterior center starting at the 22 somite stage and related to the development of the tail. (*c*) A slight mediolateral gradient beginning at the 43 to the 46 hour stage and becoming more pronounced. This may be ascribed to development in the spinal cord. (*d*) A striking concentration in any rapidly developing or growing structures at the beginning, or shortly after, the appearance of such structures. The last statement (*d*) applies to each of the previously mentioned (*a, b* and *c*) patterns.

These patterns of copper concentration parallel those reported by other investigators for the metabolic rate, cytochrome oxidase activity and oxygen uptake. Other workers have reported that copper is necessary for cytochrome oxidase production and maintenance and that in the chick embryo (one to three days of incubation) most of the metabolic activity is due to the cytochrome system. Hence, the distribution of copper ions in the early chick embryo may be associated with the cytochrome system.

REID, New Brunswick, N. J.

A STUDY OF FASCICULATIONS. HARRY A. TEITELBAUM and H. WALDO BIRD, J. Nerv. & Ment. Dis. **108**:455 (Dec.) 1948.

Teitelbaum and Bird review the experimental reports on the site of origin of fasciculations and report the results of their experiments in 4 cases—2 of progressive muscular atrophy, 1 of Jamaica ginger toxicity and 1 of encephalomyelopathy, type undetermined. Intocostrin® (purified Chondodendron tomentosum extract) abolished the fasciculations in all 4 cases; spinal anesthesia or nerve block decreased the fasciculations in the case of triorthocresyl phosphate poisoning but not in the others. Neostigmine was given in the cases of progressive muscular atrophy, in which it increased the fasciculations. The authors conclude that fasciculations originate at the myoneural junction but that in the case of Jamaica ginger poisoning there may be also a central origin.

FARMER, Philadelphia.

"Pins and Needles": Observations on Some of the Sensations Aroused in a Limb by the Application of Pressure. G. Weddell and D. C. Sinclair, J. Neurol., Neurosurg. & Psychiat. **10**:26 (Feb.) 1947.

Weddell and Sinclair studied the sensations produced in an extremity when compressed at different levels for varying lengths of time, different amounts of pressure being used. The abnormal sensations of "pins and needles" were compared with changes produced by single nerve compression, and a new pathophysiologic explanation was offered. The ordinary sphygmomanometer cuff was used, and the pressures varied from 60 to 300 mm. of mercury. The average pressure used was 150 mm., and the cuff was applied to the arm and the upper and lower parts of the forearm. In the normal subject, compression above the elbow produced a characteristic "compression tingling" in the hand, beginning between the first and the second minute and lasting an average of three to four minutes. Continued pressure led to a sensation of "velvety numbness," beginning about fifteen minutes after compression was initiated. For compression tingling, the cuff must be above the elbow, and the sensation was felt mainly in the palm of the hand and did not extend more than 2 inches (5 cm.) above the wrist. In cases of amputation of one hand a tingling was produced in the "phantom hand" identical with that perceived in the other hand. Direct pressure on the ulnar nerve produced no tingling if the circulation was not impaired. The tingling, therefore, was due mainly to stimulation by asphyxia of tactile fibers in the somatic nerves directly compressed by the cuff. "Release pricking" is a coarse, sharp pricking sensation felt predominantly in the finger tips and palm after release of the compression cuff. This sensation required at least ten minutes of compression, and the pricking lasted from five to ten minutes. The studies reveal that this sensation is conveyed by somatic pain fibers. The peripheral nerve endings are stimulated by the removal from the surrounding tissue spaces of metabolites which accumulate during periods of circulatory depression. The term "pins and needles" as commonly applied in everyday life is a loose generalization, which includes a number of different clearly defined and easily reproduced subjective sensations.

Malamud, Los Angeles.

The Pain Chart. K. D. Keele, Lancet **2**:6 (July 3) 1948.

Keele attempts to objectify the complaint of pain by establishing a time-intensity pain chart to be kept by the patient. The chart consists of an hourly recording of the degree of pain under one of four categories, as defined by the author: (1) "slight" pain (awareness of pain without distress); (2) "moderate" pain (attention distracted from a routine occupation, such as reading or housework); (3) "severe" pain (field of consciousness filled to the exclusion of other events, and visceral reflex accompaniments frequent); (4) "agonizing" pain with motor effects (evidenced by restlessness, or the syndrome of shock).

The validity of the categories was assessed by the observation of pain following known stimuli, such as surgical procedures, and typical clinical pain syndromes, such as the angina of effort and the pain of gastric ulcer. These showed typical changes in degree of pain.

Charts were made for less well understood conditions. In cases of tetany the close relation to muscular movement was clearly shown. Charts were also used to assess the response to analgesics. The author distinguishes three clinical types of pain: (1) "organic" pain, produced by pain stimuli and not modified by suggestion; (2) "psychogenic" pain, which has little or no organic basis and is maximally influenced by suggestion; (3) "mixed" pain, which combines organic and psychogenic pain in various proportions and is the commonest form met with in practice.

It was found that even in the presence of an apparently sufficient organic cause, such as carcinoma of the stomach, pain may be predominantly psychogenic. The characteristic features of psychogenic pain include (1) irregularity of occurrence with absence of evidence of organic cause; (2) response on several occasions to a placebo, such as distilled water, and (3) irregular response to potent analgesics. In 11 of 16 cases of painful organic disease there was relief of pain on the administration of distilled water.

MADOW, Philadelphia.

Neuropathology

DEPOSITION OF IRON IN PARAVENTRICULAR AREAS OF THE HUMAN BRAIN IN HEMOCHROMATOSIS. JAN CAMMERMEYER, J. Neuropath. & Exper. Neurol. **6**:111 (April) 1947.

This study is based on the findings in a case of hemochromatosis in a man aged 60. Autopsy revealed, in addition to changes in the viscera, a primary, malignant tumor of the liver with metastases in the adrenal glands. Varices in the juxtacardial part of the esophagus resulted in a terminal hemorrhage. Besides definite changes in the pituitary gland, pineal body and choroid plexus, which showed scanty focal iron pigmentation, deposits of iron were observed in several circumscribed regions of the ventricular wall. The same areas were characterized normally by the presence of melanin-containing nerve cells and a highly vascularized tissue, covered by a flat lining ependyma. The anomalous pigmentation was most conspicuous in the area postrema and pars tuberalis of the pituitary gland and was much less pronounced in the infundibular stem, the eminentia saccularis (posterior part of the infundibulum), the supraoptic crest (nucleus of the lamina terminalis), the subfornical body (intercolumnar tubercle) and the pineal recess (along the ventricular surface of the posterior and habenular commissures).

Many other changes were present in the brain. They included hypertrophy of the astroglial nuclei; small perivascular softenings in the lentiform nucleus, containing many compound granular cells with iron pigment; considerable deposits of iron in the lentiform nucleus, partly diffuse and partly intracellular, and scattered hemorrhages limited to the perivascular spaces. A few macrophages with iron pigment were observed in the leptomeninges. In the cerebellum, near the fastigium, the subependymal zone of the fourth ventricle contained deposits of iron, and the granular layer was marked by perivascular aggregations of compound granular cells containing iron and by some iron-containing astrocytes.

In hemochromatosis a definite deposition of iron occurs not only in the pituitary gland, pineal body, leptomeninges, choroid plexus and lentiform and dentate nuclei, but also in the area postrema, a rather typical feature. In various paraventricular regions of the diencephalon and telecephalon a very moderate iron pigmentation of glial and ependymal cells is noted (in the infundibulum, supraoptic crest, subfornical body and pineal recess). In the cerebral and cerebellar cortex and the ganglia of the peripheral autonomic nervous system there may be a scattered intracellular storage of minute particles of the metal.

Besides the scattered ferruginous changes in the glia and ependyma, there is encountered in the paraventricular regions a number of normal-appearing, melanin-containing nerve cells (increasing with advanced age).

The deposition of iron, which is restricted to cells acting as phagocytes, is related to structural and functional peculiarities of blood vessels in the same regions of the ventricular wall. The significance of the findings in these areas in cases of hemochromatosis is briefly discussed.

GUTTMAN, Wilkes-Barre, Pa.

REPORT OF A CASE OF DEATH AFTER PREFRONTAL LOBOTOMY. P. S. ERINGA, Folia psychiat., neurol. et neurochir. **51**:301 (Aug). 1948.

Eringa reports a case of death, occurring forty-eight hours after prefrontal lobotomy which was due to hemorrhage into the fourth ventricle. The ventricular hemorrhage was regarded as secondary, and not directly related to the operation.

ALPERS, Philadelphia.

Psychiatry and Psychopathology

OCULAR FINDINGS IN THREE HUNDRED AND TWENTY-THREE PATIENTS WITH SCHIZOPHRENIA. MARTIN COHEN, Arch. Ophth. **41**:697 (June) 1949.

Three facts in connection with schizophrenia prompted the present report: (1) the prevalence and gravity of this mental ailment, (2) the absence of recent ophthalmoscopic reports and (3) the lack of micropathologic description of the optic disk in cases of schizophrenia.

The group of patients studied consisted of 243 men and 80 women, whose ages ranged from 18 to 77 years. A neuro-ophthalmologic examination was conducted on all patients with respect to the ocular muscles, the pupillary light reaction, the gross visual fields, when possible, tension, exophthalmos, nystagmus and ptosis. These tests were of negative value, as the findings and reactions were normal, particularly the pupillary responses.

In 100 patients (31 per cent) the color of the disks was normal; 84 (26 per cent) showed a pronounced brown-gray discoloration of the temporal portion of the disk, while in 139 (43 per cent) the discoloration was diffuse or complete. These findings indicate either a pronounced temporal or a diffuse discoloration in 223 (69 per cent). This is an unusually high incidence of abnormality of color. In the older patients, the brown-gray color might be attributed to vascular changes due to arteriosclerosis, but the retinal vasculature in these patients was normal. The percentage of young and middle-aged patients with discoloration of the disks must be considered excessive, since 102 of 171 patients under 50 years of age (60 per cent) showed this brown-gray color.

The ophthalmologic manifestations and clinical findings here presented suggest the probable existence of a pathologic process affecting the visual pathways in the brain of schizophrenic patients.

SPAETH, Philadelphia.

DYNAMIC ASPECTS OF PSYCHOPATHIC PERSONALITY. WALTER BROMBERG, Psychoanalyt. Quart. **17**:58 (Jan.) 1948.

Bromberg states that the dynamic psychopathologic substrata of the so-called psychopathic personality are similar to, if not identical with, the basic defects in the structure of the ego found in a neurotic character and in "impulse neurotics." The structure of the psychopathic character rests on the same defenses against striving for forbidden instinctual gratifications from the early oral stages of infantile development as those in the neuroses. In such patients the presence of anxiety, feelings of guilt, repression of instinctual urges and substitutive gratifications makes it difficult to view the psychopathic personality as dynamically dissimilar to the symptomatic neuroses. Theoretically, then, the psychopathic personality should be a remediable condition. Bromberg believes, however, that the ever present attitudes of society toward psychopathic persons requires recognition in psychotherapy. He states that the defenses of society are so strongly entrenched and so infiltrated with punitive attitudes, and that such infinite patience and resourcefulness are required of psychotherapists, that spectacular results cannot be expected in the treatment of this neurotically ill group.

Bromberg describes the analytic treatment of a psychopathic personality and discusses the problems and difficulties encountered in the handling of such a patient. Unfortunately, the treatment was terminated before the analysis could be successfully completed.

WERMUTH, Philadelphia.

Diseases of the Brain

PITUITARY MYXEDEMA: REPORT OF THREE CASES. H. ST. G. TUCKER JR., J. L. CHITWOOD and C. P. PARKER, Ann. Int. Med. **32**:52 (Jan.) 1950.

Pituitary myxedema may be regarded as a special type of failure of the anterior lobe of the pituitary or panhypopituitarism, in which the secondary thyroid failure dominates the clinical picture. In the 3 cases here reported all the histories and physical findings were fairly typical of myxedema. Subsequent studies showed each to be an instance of primary pituitary failure with secondary hypothyroidism, together with secondary hypogonadism and deficiency of the adrenal cortex. In the histories the outstanding feature distinguishing the condition from ordinary myxedema was the loss of genital function. Extreme weakness and inability to work constituted a major complaint. None of the patients showed any pigmentation of the type seen in Addison's disease. The special features indicative of primary pituitary failure were scantiness of face and body hair and wrinkling of the skin. The testes were somewhat small or soft in each case.

All the patients showed anemia, which resisted efforts at correction until adequate hormonal substitution was achieved. The lowered basal metabolic rate was accompanied with increased serum cholesterol in 2 cases and appeared later in the third, after a lapse in administration of thyroid. The Kepler water diuresis test gave a strongly positive result in all 3 cases and offered presumptive evidence of adrenocortical deficiency. The combined use of the insulin tolerance test and the determination of 17-ketosteroid excretion was not helpful. The authors suggest that these two tests, while extremely useful, may not aid in detection of instances of partial failure of the anterior lobe of the pituitary. Roentgenographic evidence of a pituitary tumor was definite in 2 cases and strongly suggestive in the third.

The primary lesion in each of these cases appeared to be a chromophobic adenoma of the pituitary gland. The tumor was irradiated in each case, and hormonal substitution therapy was instituted simultaneously. The over-all result of treatment was considered gratifying in 2 patients. Both returned to steady work after prolonged periods of disability. Both are living normal married lives and regard themselves as well. The third patient is considerably stronger and has normal sexual function, but he still feels below par and suffers from exertion dyspnea and joint pains.

The authors believe that by the judicious combination of thyroid, adrenal cortex extract and gonadal substitution products, patients such as these can be successfully managed. A proper dosage can be arrived at only by a prolonged period of trial.

ALPERS, Philadelphia.

TUSSIVE SYNCOPE: OBSERVATIONS ON THE DISEASE FORMERLY CALLED LARYNGEAL EPILEPSY, WITH REPORT OF TWO CASES. W. S. MCCANN, R. A. BENCE, F. W. LOVEJOY JR., P. N. G. YU, R. PEARSON, E. B. EMERSON, G. ENGEL and J. J. KELLY, Arch. Int. Med. **84**:845 (Dec.) 1949.

The authors review the problem of Charcot's syndrome of laryngeal epilepsy, characterized by loss of consciousness after severe coughing and describe the laboratory findings in 2 similar cases.

Abnormally high pressures in the right ventricle during coughing were obtained in both cases studied. In the first case it was fairly well established that the syncope and convulsions resulting from paroxysms of coughing or from the Valsalva maneuver were caused by congestion of the cerebral veins, decreased cardiac output and anoxemia. In the second case, though syncope or convulsions were not exhibited while the patient was under observation, the clinical and laboratory evidence was similar to that in the first case; and it is assumed that syncope would have occurred had the patient been able to sustain either the cough or the Valsalva maneuver. Studies of the first patient to elucidate the mechanism of the pressure in the right ventricle with coughing were inconclusive. The possibility of reflex spasm of the pulmonary artery existed, in view of the fact that high pressures similar to those induced in the right ventricle with coughing were produced with a bronchoscope in the trachea.

The authors comment on the importance of nicotine inhaled from smoking in these reactions. Whether or not the excessive smoking of cigarets in both these cases permitted the absorption of nicotine in sufficient quantity to cause pulmonary vasoconstriction could not be determined.

The authors deem the term "tussive syncope" more appropriate for this syndrome than "laryngeal epilepsy," since the syncopal response is dependent on circulatory disturbances due to coughing, and is not related to epilepsy.

ALPERS, Philadelphia.

MULTIPLE SCLEROSIS (ENCEPHALOMYELITIS DISSEMINATA PERIAXIALIS) AND THE VEGETATIVE NERVOUS SYSTEM: I. GASTRIC DISORDERS IN MULTIPLE SCLEROSIS. LEO HESS, J. Nerv. & Ment. Dis. **1**:30 (Jan.) 1950.

The author cites hyperacidity, hypermotility and greatly deepened peristalsis of the stomach as almost constant features of multiple sclerosis and discusses this disturbance as a manifestation of distorted function of the autonomic nervous system. It is postulated that plaques in the nucleus dorsalis vagi or in the hypothalamus may be the site of origin of these gastric disorders.

FARMER, Philadelphia.

DIABETES INSIPIDUS FOLLOWING CLOSED HEAD INJURY. R. J. PORTER and R. A. MILLER, J. Neurol., Neurosurg. & Psychiat. **11**:258 (Nov.) 1948.

Porter and Miller reviewed 18 cases of diabetes insipidus following closed head injury. The site of trauma was frontal in 9 cases and occipital in 6 cases; in 12 cases the skull was fractured. In the majority the injuries were severe, as evaluated from the duration of post-traumatic amnesia. The onset of symptoms occurred nine to thirty-one days after injury. The degree of polyuria and polydipsia was generally mild at first and reached its maximum some days to weeks later. In 11 cases recovery was spontaneous within nine months after the onset, while in the remaining 7 cases the disease persisted from two to eight years. Treatment with posterior pituitary extract resulted in complete relief of symptoms. In the majority of cases the syndrome of diabetes insipidus was the only manifestation of hypothalamic disturbance, and the infrequency of other hypothalamic syndromes was remarkable. The only other intracranial signs were related to the commonly associated injuries of the olfactory and optic nerves. In the opinion of the authors, a traction lesion of the pituitary stalk from displacement of the brain at the time of the injury is the most likely mechanism of post-traumatic diabetes

insipidus. The duration and severity of the latter may depend on the extent of neuronal damage to the supraoptic hypophysial tract.

N. MALAMUD, San Francisco.

PRECOCIOUS PUBERTY OF INTRACRANIAL ORIGIN. CHARLES E. TROLAND and CARROLL A. BROWN, J. Neurosurgery **5**:541 (Nov.) 1948.

Troland and Brown review 12 cases of ectopic pineal tumors from the literature and add a case of their own. This case differed from the reported cases in that precocious puberty was a symptom.

Their patient, a boy aged 14 years, was admitted to the neurosurgical service complaining of loss of vision, headaches, nausea and vomiting. When he was 9 years of age the mother had noted that he seemed stronger than his older brothers. At the age of 10 years, excessive pubic hair and enlargement of the external genitalia were evident. For eight months prior to admission he had complained of progressive loss of vision in both eyes.

The neurologic status was normal except for bilateral pallor of the optic disks, more pronounced on the left; decreased visual acuity, and bitemporal hemianopsia with some constriction of the nasal field of the right eye and considerable constriction of the left. A divergent strabismus of 20 degrees was present in the right eye in all meridians. Roentgenograms of the skull showed a marked thinning of the floor of the sella turcica, with erosion of the posterior clinoid processes. The bone age of the long bones corresponded to that of persons at least 18 years old. A ventriculogram showed a defect in the anterior floor of the third ventricle. A craniotomy done in the right frontal area revealed a tumor obliterating most of the structures surrounding the chiasmal region. The histologic diagnosis was pinealoma. Roentgen therapy was given postoperatively.

It is the authors' opinion that, for the present, precocious puberty should be regarded as a multiglandular dysfunction, involving the hypothalamus, tuber cinereum and hypophysis, all of these structures having been held responsible for genital dysplasia by different authors. In the opinion of the authors, involvement of the pineal region was not responsible for the precocious puberty in their case.

TOZER, Philadelphia.

SUBCORTICAL FOCAL FORMS OF DEMENTIA PARALYTICA. ROGER REYSS-BRION, Encéphale **38**:429, 1949.

The symptoms of the acute meningoencephalitic types of dementia paralytica are classically numerous, varied, variable, diffuse and, in themselves, not particularly characteristic. In certain conditions, however, the symptoms are remarkably precise and stable, suggesting a local lesion of the nervous system. These are the "focal forms" of dementia paralytica, described by Lhermitte in 1932. The "cortical" forms of this type are the best known. In a careful review of the literature, the author notes that about 50 cases of Lissauer's cortical type of focal dementia paralytica have been reported. Among the "cortical" forms the author includes the sensory types, discussed first by Serieux.

In a survey of the literature on subcortical syphilitic syndromes, the author carefully tabulates 66 cases reported up to 1938. After eliminating cases in which the diagnosis might be questioned and those in which the condition was due to tertiary syphilis, such as gumma, he was left with 26 cases. These he divided into two series. The first comprised cases of a primarily clinical type of the subcortical syndrome, which in all probability was symptomatic of dementia paralytica. In

this group occurred symptoms of choreoathetosis, parkinsonian syndromes, contractures due to extrapyramidal lesions, chorea and writer's cramp. The second series of cases received anatomic verification showing the correlation between the clinical picture and the lesions, which were predominantly in the region of the basal ganglia. This series included symptoms of chorea, choreoathetosis, parkinsonian syndromes and myoclonia.

The author reports a case of his own, that of a woman aged 41 who had a disease diagnosed and verified as the tabetic form of dementia paralytica, with mental symptoms, hallucinations, oppositional myoclonia and dyslalia. There was no evidence of familial, congenital or acquired degenerative disease to account for the myoclonia. The myoclonia and the mental symptoms disappeared under malarial and arsenical therapy. The cerebrospinal fluids returned to normal, thus eliminating the possibility of a tertiary lesion. The author concludes that the pathologic process was a syphilitic encephalitis confined primarily to the dentate nucleus or the striate body. The dyslalia is attributed to an extrapyramidal lesion of the same type, which was irreversible, however. The hallucinatory syndrome with its regression was probably due to another area of focal meningoencephalitis at the level of the left parietal cortex. This case represented a typical example of the focal form of dementia paralytica. It was a subcortical combined with a cortical type, and as such illustrates the artificiality of rigidly separating the two types.

ZINKIN, New York.

Society Transactions

NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

Leo M. Davidoff, M.D., *President, New York Neurological Society, Presiding*

Joint Meeting, March 9, 1948

CASE PRESENTATIONS OF NEUROPATHOLOGIC CONDITIONS

Chorionepithelioma: Single Metastasis to the Infundibulum. DR. GERALD F. PERRY (by invitation).

A clinical presentation of a case of chorionepithelioma of the brain was made. Only 3 such cases had been encountered at Mount Sinai Hospital in the past ten years, 2 of men and 1 of a woman. The ages varied from 22 to 70 years. The case presented was that of a man, aged 22, with the usual symptoms of intracranial pressure leading to a diagnosis of brain tumor. Arteriographic examination and a craniotomy in the right frontal area failed to expose the tumor. Necropsy revealed a large mass completely filling the third ventricle, with only a small patent area left posteriorly at the junction of the third ventricle and the aqueduct of Sylvius. The mass was indistinguishable from the underlying tuber cinereum. The lateral ventricles were reduced to narrow slits with the wings spread out in both directions, and there was moderate dilatation of the extreme anterior ends of the ventricles. Microscopic examination of the tumor disclosed a typical chorionepithelioma.

It was pointed out that such a tumor metastasizes frequently, and, though the common site of the primary growth is the uterus, the tumor is also known to occur in the ovary, testis and other parts of the body, which are also common sites of teratomatous new growths. It was thought that a unilateral differentiation of the primordial epithelium, found in teratomas, is responsible for the formation of such tumors in extrauterine sites.

Spongioneuroblastoma: A Demonstration. DR. JOHN J. AMBLER (by invitation).

Specimens from 10 cases of spongioneuroblastoma were shown. The tumor is not rare but comprises a large percentage of true tumors of the brain formerly included under the classification of spongioblastoma or glioblastoma, and occasionally of ganglioneuroma.

Spongioblasts and neuroblasts have previously been described and recognized. Both these cells have a common ancestor in the primitive neuroepithelium. This primary neuroepithelium contains the bipotential parent cells which, on further development and maturity, may give rise to tumors of the spongioblastic series, on the one hand, or to tumors of the neuroblastic series, on the other. However, it is reasonable to assume that there exist tumors containing a mixture of spongioblasts and neuroblasts in approximately equal numbers. It is this type of tumor that can properly be termed "spongioneuroblastoma." In this demonstration, the Nissl stain was employed to bring out particularly the character of the nucleus and the tigroid bodies of the neuroblastic cells and, by this means, the

various stages of neuroblastic lineage, such as are found in the embryonic state, up to the more mature form, including cells in the process of division.

The type of tumor under discussion is no longer considered a rarity, as similar cases are constantly being reported. Recently a large number of such tumors was reported by Drs. Kuhlenbeck and Haymaker. The latter, I believe, is here tonight. I hope that he adds his opinion to those of others who are to discuss this demonstration.

Cerebral Changes Associated with Generalized Thrombocytic Thrombosis. DR. MARTIN A. GREEN (by invitation) and DR. SEYMOUR ROSENTHAL (by invitation).

Thrombocytopenic purpura with generalized thrombocytic thrombosis of small blood vessels was first described by Moschcowitz (An Acute Pleiochromic Anemia with Hyaline Thrombosis of the Terminal Arterioles and Capillaries, *Arch. Int. Med.* **36**:89 [July] 1925). Fifteen cases have thus far been recorded.

The disease occurs in all decades of life and predominantly in females. Its clinical manifestations and hematologic alterations are similar to those which may be found in any of the thrombocytopenic purpuras. In addition, however, there are a low grade fever and a hemolytic anemia, which may be severe. Symptoms referable to the central nervous system appear during the course of the disease or terminally, as either mental changes or focal involvement. There is no constant pattern of neurologic signs, but characteristically they are transitory and tend to wax and wane during the course of the illness.

The disease is an acute illness which ends fatally, usually within one to seven weeks.

Of the patients whose cases are presented here, 1 was a man aged 69 and 2 were women, both 33 years of age. The history and clinical findings were similar to those in previously reported cases. Neurologic manifestations were variable. In 1 patient they consisted of olfactory hallucinations, mixed aphasia and drifting of the right upper extremity. These symptoms, coupled with signs and symptoms referable to the lungs, prompted a diagnosis of metastatic brain tumor. Another patient was somnolent and exhibited nuchal rigidity. The third patient passed into coma terminally but reacted to painful stimuli as though there were hemihypalgesia. Death occurred in each case within three and one-half weeks after onset of the illness.

Autopsy showed thrombocytic thrombi in the terminal arterioles and capillaries of all organs. The thrombi were most constant and numerous in the central nervous system, myocardium, kidney, adrenal gland and pancreas. In the central nervous system they showed a striking predilection for the cerebral cortex. A surprising feature was the almost complete absence of parenchymatous changes. There were, however, some areas of generalized gliosis, softening and focal necrosis, with an occasional small hemorrhage, but none of these was prominent.

Both in the viscera and in the nervous system several stages of thrombus formation and organization were observed. In the earliest lesion, with the hematoxylin and eosin stain there was a loose aggregation of numerous distinct, eosinophilic, granular bodies which partially or completely occluded the vascular lumen. Other thrombi appeared as more coarsely granular, agglutinated masses. These frequently showed organization, as evidenced by swelling and proliferation of the endothelial cells, with invasion of the thrombus by these cells. These organizing thrombi were apparently older lesions. Weigert's stain for fibrin and

the phosphotungstic acid hematoxylin stain demonstrated small amounts of fibrin in some thrombi. The benzidine stain showed that the thrombi were not composed of red blood cells or products of their disintegration.

The cause of the thrombocytopenia and the mechanism of the thrombotic phenomena are not known. Most observers agree that the endothelial proliferation is a secondary reaction to the presence of the thrombus, rather than an initial process which may cause thrombosis. This view is supported by the following observations in the present cases: (1) Endothelial proliferation was found only in vessels containing thrombi, and (2) thrombi were present in vessels which did not exhibit endothelial proliferation.

DISCUSSION OF CASE PRESENTATIONS

DR. HARRY M. ZIMMERMAN (by invitation): I was greatly interested in the location of the chorionepitheliomatous metastasis in the first case presented this evening, for it is this type of localization, rather than the tumor itself, that is of neurologic interest. I recall once seeing a small metastasis of a tumor of the ovary in the infundibulum with symptoms of diabetes insipidus; I wonder whether Dr. Perry's patient had any neurologic signs referable to the site of involvement. I was a bit amused by the reference to Askanazy's case of primary chorionepithelioma of the brain. I did not think any orthodox pathologist would accept this case as proof that this tumor arises in the brain. It is well known that, in adults especially, microscopic chorionepitheliomas in the testis are overlooked; unless a neoplasm is searched for at autopsy, one cannot conclude from the finding of a tumor only in the brain that the growth is primary there.

I hesitate to say anything about the second paper, for I am one of those persons who are still skeptical about neuroblastomas in the nervous system. I have seen tumors of spongioblastic type with ganglion cells easily identifiable in the gliogenous neoplasm. When these ganglion cells are identifiable by the Nissl technic on the basis of tigroid substance in the cytoplasm, when the nucleus is of the large, "fish eye" variety, as illustrated here, and when the nucleus has a prominent large round nucleolus, then it seems to me that if they are tumor cells they are not neuroblasts but gangliocytes. These normal ganglion cells can be entrapped in a gliogenous tumor which grows in among them. On the other hand, if trigroid substance is absent, and if the diagnosis is based on the morphologic appearance of the nucleus and its nucleolus, one bases the diagnosis on very slight evidence. I do not feel that a nucleus of the type shown this evening is necessarily diagnostic of a ganglion cell and its precursor, the neuroblast. I have seen many ganglion cells in gliogenous tumors and many cells which look very much like those shown here, and I cannot deny, but I would also refuse to accept, the statement that because of them the tumor represents a spongioneuroblastoma. Every student of morbid anatomy knows how fallacious can be a diagnosis which is based entirely on morphologic similarities. Is it not better, perhaps, in this type of tumor to study the biologic and behavioral characteristics in such a place as the eye of a heterologous animal? Cannot transplants of this tumor be made into the anterior chamber of the eye of a guinea pig or a rabbit, in the hope that these cells will mature and take on the characteristics of ganglion cells which all could agree are ganglion cells? Cannot brain tumors be produced experimentally in mice, in which large numbers of such inoculations may be made, and transplantations of these tumors be made to other mice and into the anterior chambers of the eyes of other animals, to see whether true neuroblasts can be identified in such tumors? I must say that such experiments as I have just indicated have in my hands

always given negative results. I have never yet convinced myself that portions of a tumor when transplanted into the anterior chamber of the eye of different species have yielded what any one would be willing to accept as neuroblasts or precursors of ganglion cells. The method is feasible, for it is possible from a tumor in which there are mixed components, such as oligodendrocytes, spongioblasts and astrocytes, to grow the different cell types in pure culture in the anterior chamber of various animals. Why cannot the same thing be done with the neuroblast?

Much has recently been written on thrombocytopenic purpura with thrombocytic thrombi that develop in vessels. I should like to ask Dr. Green whether he has ever seen any evidence of perivascular cerebral injury. Fitzgerald, Auerbach and Frame *(Blood* **2**:542 [Nov.] 1947) showed pictures essentially like those presented this evening. They called attention to the thrombocytic thrombi in the cerebral vessels, but neither their pictures nor those shown this evening seem to contain any evidence of encephalomalacia or long-standing damage. I wonder whether these occlusions are really not of the agonal type.

Dr. Arthur Weil (by invitation): Usually case presentations are the stepchildren of meetings, and one is glad when they are over and one gets to the main topic; but Dr. Zimmerman's discussion shows that one can learn much even from single cases and that they open pathways to new ideas and bring up controversies which require intensive study. I wish to comment on the primary occurrence of chorionepithelioma in the brain. I am aware that I shall be open to ridicule if I express the opinion that the tumor shown by Dr. Perry may be a primary chorionepithelioma; however, I am in good company. Dr. Perry mentioned the paper by Askanazy (Teratom und Chorionepitheliom der Zirbeldrüse, *Centralbl. f. allg. Path. u. Path. Anat.* **17**:872, 1906). Askanazy described 3 cases of chorionepithelioma which occurred in the pineal gland. The tumors were not connected with a pinealoma, but in all 3 cases there was pubertas precox, and he pointed out that pubertas precox, the early development of sexual characteristics, was not due to the pineal gland but was produced by the teratomas, which, as is now known, produce prolan, a chorionic gonadotropin. Askanazy, in his 3 cases, made a careful study of the testes, and could not find any primary chorionepithelioma there. Of course, as Dr. Zimmerman pointed out, sometimes such testicular tumors are minute and can be overlooked, like other primary tumors, e. g., primary carcinoma of the lung, which may reveal itself first as a cerebral tumor and only later is detected as a small nodule in the lung. Dr. Perry emphasized that there was no clinical sign of testicular disease in this case. In the region of the infundibulum there must be cells which produce gonadotropic hormones, in the anterior lobe of the hypophysis, and therefore it is possible that cells of this type undergo neoplastic disease and form a tumor. This hypothesis cannot be proved at present, but the possibility exists that chorionepithelioma may arise primarily in this region.

As to the second paper, I shall have to say again what I said in a discussion of a case which Dr. Globus presented at the annual meeting of the American Association of Neuropathologists in 1947. Dr. Zimmerman commented that the negativistic attitude toward the acceptance of this classification was supported by the finding within the tumor of original neurons and normal ganglion cells which had been surrounded by the rapidly growing tumor. But one should ask why normal neurons may be multinucleated or why this type of tumor cells may show mitotic figures. Dr. Ambler did not emphasize this feature, but it was definite in 1 case, in which three nuclei in one large cell had undergone mitotic division.

As to the third case, I wonder whether one should classify it with the thrombocytopenic anemias. Certainly, there was no paucity of thrombocytes. The thrombi were formed mostly by thrombocytes. The nature of this thrombus formation reminds one of the thrombi which one finds after operation. Aschoff, I remember from my student days, produced experimentally such white thrombi in which the outer part of the core was formed by thrombocytes, and he pointed out that slowing of circulation, together with a lesion of the endothelial wall, might bring about this type of thrombosis. Furthermore, he pointed out that in any type of lesion of the endothelium, cephalin, which is now considered as thromboplastin, might be produced and give rise to sudden thrombus formation. Dr. Green pointed out that it could not possibly be an inflammatory lesion of the endothelium which was responsible for the production of thrombi, because he did not find them in blood vessels of the body or brain where no thrombi had been formed. But either one can argue *post hoc, ergo propter hoc:* Thrombi were formed in this endothelial lesion, or proliferation of the endothelium follows thrombus formation, as he described it.

DR. LEWIS D. STEVENSON: I shall attempt to discuss only Dr. Ambler's paper. Anyone dealing with large numbers of brain tumors knows that chorion-epitheliomas form a special group of tumors. Since they seem to contain elements derived from the spongioblasts and others which come from neuroblasts, the term spongioneuroblastoma means something. Obviously, these cells are tumor cells, and they are not fully developed ganglion cells; as Dr. Weil points out, they are multinucleated; so one can hardly say that they are normal cells which have been surrounded by spongioblasts.

The point I should like to have Dr. Ambler or Dr. Globus discuss is this: One of these large cells, when stained by the Nissl method, has a clear nucleus and a dark-staining nucleolus. It has seemed to me, in some of my own preparations, in which I have tried to cut a section as near this as possible, that the same cell stained with silver carbonate will not have such a prominent nucleolus and will have definite prolongations that strongly suggest a spongioblast. Is this a cell which has some features of a neuron and some features of an astrocyte or a neuroblast and the spongioblast at the same time?

DR. WEBB HAYMAKER (by invitation): If the majority of the cells which Dr. Ambler showed are not of the neuroblastic series, I do not know what else to call them. They have characteristics identical with those of neuroblastic cells: large nucleus, nucleolus and, in some instances, multipolar cytoplasmic processes. About a year and a half ago Dr. Kuhlenbeck and I (*Mil. Surgeon* **99**:273 [Oct.] 1946) published a series of these tumors. In 1 case the tumor was relatively small and occupied mainly the internal capsule, where there were many neoplastic nerve cells. In another the neoplastic nerve cells were in the cerebellum and were derived from the Purkinje cells; such cells were migrating out into the molecular layer and into the meninges, which they massively invaded. These cases illustrate two points which should be taken into consideration in deciding whether nerve cells in brain tumors are neoplastic or normal, that is, the position of the tumor and the nature of the cells from which the tumor is derived. During the last year or so we have had a few tumors similar to those shown by Dr. Ambler, and therefore I am inclined to believe that they are of fairly frequent occurrence.

DR. J. H. GLOBUS: I shall first answer Dr. Zimmerman's question regarding the metastatic lesion in the infundibular region. The clinical diagnosis was that of a tumor in that region, because the clinical manifestations included those of diabetes insipidus and the neurologists at the Mount Sinai Hospital were fully aware of the significance of symptoms of this type.

As to the spongioneuroblastomas, the aim was to demonstrate and to document their existence by means of preparations of tumors of this type. You were not asked to believe; you were asked to look at the preparations and to decide for yourselves whether or not these cells are of the neuroblastic type. There is no other way of identifying neuroblasts than by their shape and the character of their nuclei and nucleoli. When one considers the extremely large cells, which are never encountered in the normal brain—cells with three or four nuclei, cells in the process of division, splitting into four or more smaller cells, conditions never seen in normal mature brain cells—there is nothing left but to decide that these cells are neuroblasts and that they constitute a major quota of the cells in the neoplasm under discussion. Assuming that these cells are neuroblasts and that the other cells are spongioblasts, there is but one conclusion, that the tumor containing these two cell types is a spongioneuroblastoma. Those who are familiar with neuropathologic material and have studied intracranial neoplasms in large numbers will agree with us that there are tumors in which spongioblasts and neuroblasts coexist and that the name spongioneuroblastoma for such neoplasms is most appropriate.

A question was asked regarding the third presentation, whether there were changes in the brain in and about the blood vessels; I think Dr. Green pointed out that the changes about the blood vessels were minimal and scattered. Only an occasional area of acute softening and an occasional aggregation of glial cells were seen.

Dr. Stevenson asked about the cell which cannot be fully identified as a neuroblast or a glioblast: I would recall to Dr. Stevenson his own opinion regarding similar cells in tuberous sclerosis. Indeed, with cells of this variety it is difficult to decide whether they belong to the spongioblastic or to the neuroblastic series. Occasionally one is fortunate in finding fibrillae running through the cell in Bielschowsky or Cajal preparations and can conclude that they are neuroblasts. It is possible that many of these cells are of the bipotential variety. Although the bipotentiality of a cell is to be regarded in the nature of its being destined to become a spongioblast, while a similar neighboring cell will be a neuroblast, the bipotentiality applies not to an individual cell so much as to a group of cells within the same restricted zone. Thus, a given cell may become a neuroblast and another a spongioblast; a single cell, except the most primordial one, will not give rise to a spongioblast and a neuroblast at the same time by division.

Clinicopathologic Study of Five Fatalities Resulting from Exposure to Simulated High Altitudes in Decompression Chambers. DR. CHARLES DAVISON and DR. WEBB HAYMAKER (by invitation).

During the recent war years, many thousands of airmen were subjected to lowered barometric pressure in decompression chambers for purposes of indoctrination into high altitude flying, and, although bends and other symptoms of decompression illness were of fairly frequent occurrence, death ensued in only 5 cases. The ages of these men varied from 22 to 39 years. Physical examinations before the "flights" revealed no abnormalities. The simulated altitudes reached were between 30,000 and 38,000 feet (10,000 and 12,600 meters). The administration of pure oxygen was begun when an "altitude" of 10,000 feet (3,300 meters) was attained.

Symptoms developed during the "flights" in all 5 cases; bends occurred in 2. Localizing symptoms of damage to the central nervous system were observed in 4; these included diplopia (3 cases), objective paralysis of the extraocular muscles (1 case), early dilatation of one pupil (1 case), weakness of the right arm (2 cases),

hemiplegia (1 case), incoherent speech or aphasia (2 cases), thrashing movements of the arm and leg unilaterally (1 case) and convulsive seizures (2 cases). In the instance in which neurologic disorders were not observed there was early shock, and in the others shock was also a striking feature. The duration of the illnesses varied from ten to fifty-five and a half hours.

Postmortem studies revealed the following changes: In the viscera, vascular engorgement and edema, especially of the lungs, were conspicuous, and the amount of pleural fluid was as high as 1,300 cc. In 1 instance there were necrosis of the heart muscle, lower nephron nephrosis and tubular degeneration of the adrenal cortex. Congestive phenomena and diapedesis of erythrocytes were prominent in the meninges. Changes in the brain were characterized by dilatation of perivascular spaces, spotty perivascular glial proliferation in preparations stained by the Holzer method, patchy perivascular demyelination, swelling of axis-cylinders and ischemic changes in nerve cells of the cerebral cortex, especially in lamina 3. Less frequent were perivascular hemorrhages in the wall of the third ventricle; disintegration of erythrocytes, both intravascular and extravascular; deposition of blood pigment in ganglion cells and glia; peculiar pigmentary changes in the thalamic ganglion cells; thrombus formation; perivascular lymphocytic infiltrates, and acute ganglion cell changes in Sommer's sector of the hippocampus. The spinal cord, available in 1 case, showed hemorrhages similar to those in caisson disease.

All 5 fatal cases are regarded as instances of aeroembolism, in which plugging of cerebral vessels by nitrogen bubbles caused hypoxic changes in the parenchyma and, as a consequence, severe shock and death.

DISCUSSION

DR. ARTHUR WEIL, Chicago (by invitation): There is a large literature on the experimental lesion in the central nervous system produced in high altitude pressure chamber experiments on animals, but this is the first time that such an excellent series of experiments on man has been brought from the Army Institute of Pathology in Washington. Of course, there are many aspects of such an experiment, both anatomically and pathophysiologically. The question arises: What is the primary cause of this lesion? It is generally assumed that it is an anoxic anoxemia, or lack of oxygen due to decrease in the oxygen absorbed in the blood, in both plasma and red blood cells. But if one takes this one-sided view, one may overlook many other factors which are contributory and which may explain why such a short interval of abnormal atmospheric pressure as that in these experiments led to such intense damage to the central nervous system. First, there exists not merely local cerebral anoxia, but a process involving all other organs of the body. Recent experiments have shown that in such a sudden reduction of atmospheric pressure there is an intense struggle between the myohemoglobin and the blood hemoglobin to take possession of the available oxygen, and the little oxygen which is circulating in the blood is mostly taken up by the myohemoglobin and the damage to the brain becomes intense. Second, such changes in atmospheric pressure influence the fermentative systems, the colloidal makeup of the central nervous system. Experimentally, one can destroy the action of ferments by submitting them to sudden high or very low pressures, and it is possible that such effects also take place in the internal mechanism of the neuron. Therefore it is not only the anoxia which is responsible for these changes, but many other factors.

Dr. Davison brought out the point that in caisson disease similar changes occur, but I should like to note that there one is dealing with a different picture, a sudden

reduction of very high pressure, from 8 to 10 atmospheres to 1 atmosphere. The old German literature is full of neuropathologic studies of caisson disease, and it was assumed that the sudden liberation of nitrogen led to bubble formation and so produced an occlusion anemia and other sequelae, similar to the reduction of atmospheric pressure in altitude flying. I think that under conditions of decompression at high altitudes the opposite also occurs. There is a lack of absorbed nitrogen and oxygen in the blood, which on the descent, and with increased pressure, gradually returns to the plasma.

The pathologic lesions teach a good lesson to the neuropathologist, for they come from human material. Present day ideas of the reaction of nerve tissue to damage have been derived mostly from animal experimentation and autopsy reports, in which one was never sure of the time which had elapsed between the damage and death; but here one sees that seventeen hours after the beginning of the experiment there was cellular proliferation of glia, building up of a fibrous glial wall, compound granular corpuscles taking up products of degeneration and swelling of the glia, axis-cylinders and myelin sheaths. One therefore must revise one's idea derived from the textbook figures and bear in mind that such a defensive reaction, which was thought to occur days, or at least thirty-six to forty-eight hours, after the damage, starts much earlier. From the medicolegal point of view, this is important. Of course, if one is a skeptic, one might say that perhaps this perivascular round cell infiltration may have been there before, that these young persons were not healthy men but had some disease which made them more susceptible. On the other hand, the repetition of this lesion in the 5 cases may exclude such an objection.

Dr. Leon Roizin (by invitation): Some of the neuropathologic features illustrated so well by Dr. Davison are interesting because they also indicate that in some conditions of anoxia involving the central nervous system the pathologic processes are distributed according to a certain pattern. A somewhat similar type of topographic distribution of the neuropathologic changes was observed by us, and other investigators, in experimental animals and in human beings subjected to prolonged and repetitive insulin coma and in some cases of pernicious anemia and pernicious malaria. Dr. Zimmerman reported similar phenomena in his studies of thiamine deficiencies (*A. Research Nerv. & Ment. Dis., Proc.* **12**:51, 1943), and Ferraro and I observed them in experimental inanition (*J. Neuropath. & Exper. Neurol.* **1**:81 [Jan.] 1942). There is much evidence that the brain obtains energy for its activities chiefly from the oxidation of carbohydrates, in which thiamine plays an important role. In these metabolic disorders one is impressed by the fact that the neuropathologic processes involve, in addition to some cortical areas, the hypothalamus, Sommer's sector of the cornu ammonis, the quadrigeminal bodies and the vestibular nuclei.

Dr. Lewis D. Stevenson: Was there an accumulation of fat in the nerve cells beyond the normal amount for the age of the patient?

Dr. Webb Haymaker: The sudan III stain failed to reveal fat in the nerve cells in any of the cases.

Dr. Weil raised the question of the relation of hypoxia to decompression illness. It is quite true that there is a considerable decrease in partial pressure of oxygen in the blood at 38,000 feet when pure oxygen is inhaled, but this in itself is not regarded as the primary cause of death, for the simple reason that in these pressure chambers runs other men (5 to 19) subjected to the same conditions simultaneously in the same chambers failed to exhibit any untoward symptoms. The fact that 800,000 to 1,000,000 men were subjected to this pressure during the war years attests to its relative safety.

The problem resolves itself into a consideration of why these particular 5 men succumbed. They were all in excellent health. So far as we are aware, there was only one factor in common among the men, and that was the amount of their adipose tissue: One was obese; 1 was slightly obese, and the other 3 were heavy set and muscular. It is known that nitrogen is five to six times as soluble in fat as in body fluids and that in the average man, whose body has a fat content of 15 to 20 per cent, about one-half the nitrogen is dissolved in fat. The fat acts as a reservoir and gives up its nitrogen into the blood stream on decompression at high altitudes. It follows that an obese person would give off relatively more nitrogen on decompression than a lean one and therefore would be more liable to the development of aeroembolism, as has been shown conclusively in the case of divers and workers in caissons. Since many other factors are concerned in decreased individual tolerance to lowered barometric pressure, none of which are known to have existed in the 5 men, the importance of the adiposity in the fatal outcome can only be surmised.

Dr. Davison mentioned that perivascular collections of lymphocytes were observed in 2 of the brains. I should like to point out that these were regarded as a part of the pathologic picture, since they have been observed by Colonel Lewis and me, to about the same degree, in 33 of 75 fatal cases of acute high altitude hypoxia occurring in airmen during the recent war.

Massive Hemorrhage in Brain Tumors. DR. SIDNEY W. GROSS and DR. MORRIS B. BENDER.

Four cases were presented, in all of which gross hemorrhage was associated with a brain tumor. The authors then cited Oldberg, who reviewed 832 consecutive cases of glioma of the brain and observed gross hemorrhage in only 31, or 3.72 per cent (Hemorrhage into Gliomas, ARCH. NEUROL. & PSYCHIAT. **30**:1061 [Nov.] 1933). Of these 31 cases, only 7 had striking features, such as sudden onset or acute exacerbation of symptoms. The authors stated that their 4 cases did not warrant sweeping conclusions in refutation of Oldberg's findings, but were of sufficient interest to be reported.

The onset in all 4 cases was sudden and in 3 was preceded by a minor head injury. In 3 cases the tumor was a malignant glioma, and in 1, a metastatic carcinoma primary in the stomach.

From the size of the tumor in each case, it is apparent that the growth must have been present for some time prior to the onset of symptoms. In all 4 cases the hemorrhage was of sufficient size to have caused sudden onset of symptoms. In 3 cases trauma may have been a factor; 1 patient bumped her head, and 2 fell, injuring an extremity. The authors felt it was conceivable that a blood vessel weakened by disease might rupture as a result of trauma, even though the trauma was not direct.

DISCUSSION

DR. IRA COHEN: Massive hemorrhage into a brain tumor is a diagnosis oftener made than verified, and oftener found than suspected prior to operation. As Dr. Gross has pointed out, Dr. Oldberg's work has shown that the diagnosis should not be made as often as it was. On the other hand, a paper by Globus and Sapirstein (Massive Hemorrhage into Brain Tumor, *J. A. M. A.*, **120**:348 [Oct. 3] 1942), based on autopsies in 94 cases of brain tumor, not solely gliomas, which had not been treated showed that hemorrhage occurred in about 10 per cent of these tumors. The 4 cases presented by Dr. Gross and Dr. Bender are rather typical of what one would look for in cases of massive hemorrhage into a brain

tumor in that there were a sudden onset and, in at least 3 of them, changes in the state of consciousness, xanthochromic spinal fluid and, as an additional factor in 3, trauma. One may, however, find large collections of blood and clots in cases without the catastrophic onset which leads one to suspect a massive hemorrhage, cases in which undoubtedly, prior to operation, there had been bleeding from time to time, so that at the operating table one will find 30 cc. or more of old dark blood and clots. In my experience, this has been most frequently seen in tumors of the blood vessel group, the hemangiomas. In fact, I reported a small group with hemorrhage into them. Likewise, in cases in which a neoplastic cyst communicated with the ventricle I have seen bleeding into the cyst. In 1 case the diagnosis of spontaneous subarachnoid hemorrhage was made during an attack. Whatever the preoperative diagnosis may be, the importance to us as surgeons and to the patient is that at the operating table we recognize that hemorrhage found in the brain is not necessarily a spontaneous hemorrhage, but may be a hemorrhage into a tumor, and that we should guide ourselves accordingly.

DR. PETER G. DENKER: I should like to say a word about the possible medicolegal importance of these cases. As Dr. Gross mentioned, in 2 of these cases the patient struck his head. In the past six months I have had occasion to give an opinion on the possible relation between trauma to the head and rapid death following such trauma. In one case autopsy revealed that the patient had a hemangioendothelioma of the brain in which hemorrhage had occurred. The patient, a girl aged 16, had struck her head as she was getting up from bending under a ledge; within twelve hours she went into coma and died within five days. On gross examination the hemorrhage seemed so large that the medical examiner thought at first it was a pure subdural hematoma, but on section it turned out to be a hemangioendothelioma; the spinal fluid was xanthochromic. Such cases are important because, though there was no question of an underlying tumor having been present for a long time, it is conceivable that a blow to the head might cause rupture of a vessel, especially in a tumor of vascular type.

In the other case the patient was in a taxicab which suddenly stopped short, and he was thrown forward, striking his head. He went into gradually progressive coma. He was brought to the Neurological Institute, and operation revealed a pituitary tumor in which there was no sign of hemorrhage. No injury to the skull or extracerebral bleeding was observed at autopsy. Was there any relation between the head injury and rapidly ensuing death, due to an admitted pituitary tumor in this case? I wonder whether Dr. Gross could clarify the relation of trauma to the head and rapidly ensuing death thereafter, even though brain tumor is present.

DR. GEORGE H. HYSLOP: Dr. Denker's comments are *apropos*. The issue is not always simple. One first must be sure of the time relation of any injury to the onset of symptoms implying an intracranial or cerebral lesion. One must also keep in mind what is known about the duration of the physiologic reaction to trauma to any part of the body which may have an effect on circulation in the brain. Direct violence to the skull not producing a concussion or comparable immediate cerebral reaction may effect momentary or transient changes in blood pressure and circulatory flow, with no organic change and with return to normal within a few seconds or a little longer. Muscular effort, including that incidental to involuntary protective efforts in the course of a fall, may bring about similar momentary physical alterations in cerebral circulation and the blood pressure level. In such instances, when there is a time lag of hours or days before there is evidence of a focal organic reaction in the brain, one is not justified in regarding the trauma as the true cause of the organic cerebral disease.

The third thing to consider is that persons with organic disease of the brain, especially those with chronic arteriosclerosis preceding a trauma, may experience a disproportionate effect from trauma.

I have been struck by the frequency with which persons with organic disease of the brain not due to trauma report what are apparently minor accidents not long before their cerebral disease becomes manifest. This has held true in cases with no medicolegal factors. I have concluded that in many of these instances the accident occurred because of functional defects; that is, while the organic damage has produced no subjective complaints and the patient is as yet unaware of subclinical alteration of function, he cannot use his body normally and is therefore prone to certain types of accidents. Whether such an accident can have any precipitating effect or whether it may alter the course of the organic disease can be determined only by a knowledge of all the relevant facts.

DR. E. D. FRIEDMAN: In my own experience, gross hemorrhage into a tumor of the brain is rare. In most cases tiny hemorrhages are seen scattered through the tumor or at its periphery, but gross hemorrhage into the tumor is rare. This is particularly true of the glioblastomas, or spongioblastomas. I believe the symptoms suggestive of hemorrhage in cases of brain tumor are due to acute interference with the whole glial system, which is concerned with the escape of fluid into the blood vessels. Arien Kappers designated the glial system as the lymphatic pathway of the nervous system. In cases of tumor, therefore, one encounters enlargement of the homolateral hemisphere. The acute onset of symptoms in brain tumor—apparently out of a clear sky—is due to the acute aggravation of edema of the brain. The sudden accession of fresh edema may thus produce an explosion of symptoms in a hitherto unsuspected lesion of the brain.

DR. S. W. GROSS: Our purpose in bringing these cases to your attention was to confirm the experience of most observers that sudden onset of symptoms in brain tumor is rarely due to a massive acute hemorrhage into the tumor. Although 4 cases with massive hemorrhage into a brain tumor were observed during a relatively short period, we believe that such cases are most unusual and that the correct diagnosis is rarely made prior to surgical exploration.

PHILADELPHIA NEUROLOGICAL SOCIETY

Sherman F. Gilpin Jr., M.D., *Presiding*
Regular Meeting, Feb. 27, 1948

Treatment of Unbearable Pain by Mesencephalothalamotomy. DR. ERNEST A. SPIEGEL and DR. HENRY T. WYCIS.

In the region of the superior colliculi, a relatively small lesion can interrupt the pain impulses ascending from the spinal cord, as well as those from the area supplied by the trigeminal nerve. However, the usual technic of exposure of the midbrain by elevation of the caudal part of the cerebrum, as carried out, for instance, by Walker for mesencephalic tractotomy, may sometimes cause considerable damage to the occipital lobe, even in the hands of the most skilful neurosurgeon. By means of the stereotaxic technic developed by us (*Science* **106**:349, 1947), this region may be reached easily without the necessity of raising the cerebrum. A fine needle electrode is introduced exactly at the desired coordinates of the skull, and the spinothalamic tract and/or the adjacent trigeminal systems may be destroyed by electrocoagulation, with only minimal injury to the overlying cerebral structures.

Experience with bilateral anterolateral chordotomy has shown that severance of the long pain-conducting systems by bilateral section of the spinothalamic tract is sometimes insufficient to eliminate pain arising in the area of the spinal nerves. Such failures may be explained by the existence of other systems, particularly chains of short neurons in the reticular substance, presenting a by-path for the conduction of pain to higher centers (Karplus and Kreidl, Spiegel and Abuel). Therefore, one must bear in mind that interruption of the spinothalamic tracts in the midbrain may sometimes be insufficient to produce relief from certain types of pain. With regard to the secondary trigeminal pathways, not only the crossed fibers found in the vicinity of the spinothalamic systems, but also uncrossed fibers in the reticular substance may play a part in the mediation of pain impulses. In addition to anatomic factors—the existence of auxiliary pain-conducting pathways—psychic factors, such as the mental attitude of the patient, his anxiety and the fixation of his attention on the pain, may play a part in the persistence of pain after interruption of the main pain-conducting pathways. One is confronted, therefore, with the question of how one could bring relief to a patient suffering from pain that is not completely relieved by interruption of the chief pain-conducting systems. Recent experiences by Freeman and Watts have shown that prefrontal lobotomy may leave the perception of pain intact, but that the patient's attitude to the existing pain may be changed in that he becomes indifferent to the pain and thus obtains a measure of relief, although the perception of pain is still present. It occurred to us that a similar effect may be obtained by placement of a lesion in the nucleus medialis dorsalis thalami. Since we were able in patients with certain psychoses and obsessive tension states to produce by medial thalamotomy (electrocoagulation of parts of the nucleus medialis dorsalis thalami) therapeutic results similar to those observed after prefrontal lobotomy, it seemed possible to replace prefrontal lobotomy with this less drastic procedure in treatment of unbearable pain. Lesions of the medial thalamic nucleus can be produced by the stereotaxic technic with only minimal injury to the overlying cortex and white matter of the cerebrum, so that many of the undesirable by-effects of the prefrontal lobotomy may be avoided. Thus, a method has been developed which may be called mesencephalothalamotomy; it consists in combined interruption of the spinothalamic tract, or, in cases of facial pain, of the secondary trigeminal pathways in the mesencephalic tegmentum (alone or together with the spinothalamic system), and lesion of the nucleus medialis dorsalis thalami (unilaterally or bilaterally). While the lesions in the midbrain are supposed to interrupt at least the main afferent pain-conducting pathways, the thalamic lesions tend to produce a relative indifference to pain perceived by way of the remaining auxiliary afferent systems. Owing to the close proximity of the superior colliculus and the nucleus medialis dorsalis thalami, the two regions may be reached through the same trephine opening.

Demonstration of a Case of Facial Pain Relieved by Mesencephalothalamotomy. Dr. Henry T. Wycis, Dr. L. Soloff (by invitation) and Dr. Ernest A. Spiegel.

A white woman aged 47 had onset of a lightning-like pain in the right side of the face in November 1940. Use of morphine, applications of local heat, inhalations of trichloroethylene and extraction of nine teeth, recommended by her physician, failed to relieve her. In April 1941 another neurosurgeon produced relief of the pain by a nerve block for five weeks, but two subsequent injections did not affect the pain. After the nerve blocks the sensation of a roaring noise developed in the right ear. In September 1941 the same neurosurgeon apparently performed a retrogasserian rhizotomy by the conventional Spiller-Frazier approach. After the

operation the pain became severer and lasted for longer periods. Chewing aggravated the pain. She stated that after operation a purulent discharge had developed in the right eye. She wore a dressing for one month. When the dressing was removed, she noticed diminution of visual acuity in the right eye.

We first saw the patient in September 1947. Examination disclosed a thin, undernourished woman, who refused to eat because of pain. She was confined to her bed because of weakness and inanition. The right side of the face was anesthetic, and the temporal and masseter muscles were atrophied on the right side. There was diminished visual acuity in the right eye. The patient was prepared for mesencephalothalamotomy as follows: A roentgenogram of the skull having revealed the presence of a calcified pineal gland, a plaster cast of the skull was made, and a roentgenogram was again made with the stereotaxic apparatus assembled to the cast. The position of the pineal gland relative to the coordinates of the stereotaxic apparatus was determined. From these data, the levels and depths of punctures necessary for coagulation of the spinothalamic tract, the secondary trigeminal pathways and the dorsomedial thalamic nucleus were computed, with the aid of specimens sectioned in the frontal plane of the stereotaxic apparatus.

Mesencephalothalamotomy (October 30).—With the use of local anesthesia, a trephine opening was made, exposing the superior longitudinal sinus. The stereotaxic apparatus was applied to the casted ring and the needle introduced into the brain at the desired levels and depths. Three punctures (five lesions) were made in the region of the right dorsomedial nucleus of the thalamus, and two punctures (eight lesions), in the region of the spinothalamic tract and secondary trigeminal pathways at the level of the superior colliculus on the same side.

Two hours after operation the patient stated that her pain had entirely disappeared. There was impairment of all forms of sensation on the right side of the body below the face. On the fifth postoperative day she was still without pain. Slight paresthesia occurred at infrequent intervals on the right side of the upper lip. There was only very mild impairment in the movements of the right toes and ankle. Motor function here had completely recovered by the ninth postoperative day. Sensation to light touch, heat, cold and pinprick was impaired on the right side (with less impairment on the medial aspect of the right side). She was discharged on the ninth postoperative day, free from all pain. The roaring noise in the right ear had ceased.

Reexamination four months after operation revealed that there was no recurrence of her former pain. There was a mild right-sided Horner syndrome. The right side of the face was anesthetic from the retrogasserian root section, and the corneal reflex was absent on the same side. Audiometric examination showed normal hearing bilaterally. There was slight intention tremor in the right hand, more pronounced than in the left. Coordination tests were well performed on each side. Sensory impairment on the right side had regressed to involve only a small elongated oval area of analgesia over the anterior aspect of the right thigh. Quantitative differences, however, particularly over the finger tips, could still be demonstrated by algesimetric readings, more pressure being required to elicit pain on the right side than on the left. The rest of the sensory status was normal.

DISCUSSION

DR. H. T. WYCIS: I shall now bring the patient in for your observation. (The patient was brought into the room.)

DR. A. M. ORNSTEEN (to the patient): Would you tell us what kind of pain you had before the operation—where it was and what kind of pain it was?

PATIENT: I had very sudden pain, pain that knocked my head back, like lightning in the sky.

DR. A. M. ORNSTEEN: Where was the pain?

PATIENT: Down here, in here, in there; sometimes here (indicating the right side of the face).

DR. A. M. ORNSTEEN: It would come all of a sudden?

PATIENT: That is right, without any warning.

DR. A. M. ORNSTEEN: How often would it come?

PATIENT: Sometimes dreadfully often.

DR. A. M. ORNSTEEN: Every hour?

PATIENT: Every hour? More than that sometimes.

DR. A. M. ORNSTEEN: All day?

PATIENT: That is right.

DR. A. M. ORNSTEEN: How long had you had it before the operation?

PATIENT: Well, I can't remember when I didn't have it.

DR. E. A. SPIEGEL: When did it start?

PATIENT: In 1940.

DR. A. M. ORNSTEEN: You were operated on in 1947?

DR. E. A. SPIEGEL: The first operation you had was in 1941?

PATIENT: That is right.

DR. H. T. WYCIS: She had the first operation in September 1941. Seven years elapsed before the other procedure was carried out.

DR. A. M. ORNSTEEN: Pain was in the forehead, the malar region and sometimes in the upper lip.

PATIENT: Sometimes it started here and followed the shape of my face. Sometimes it went as far as that, but always it was up in here (indicating).

DR. A. M. ORNSTEEN: You had it for seven years except for the short time you were relieved as a result of the other operation?

PATIENT: That is right.

DR. A. M. ORNSTEEN: You are very happy about it?

PATIENT: Yes, sir. (The patient was excused from the room.)

DR. MICHAEL SCOTT: I think we all agree that Dr. Spiegel and Dr. Wycis should be congratulated on a pioneer presentation. Any procedure which is carefully thought out along neurophysiologic lines, worked out carefully in the laboratory and then applied clinically is worth while.

To the best of my knowledge, this stereotaxic apparatus has never before been applied to a human being. The procedure which the authors have devised offers great possibilities and perhaps in the future will displace some of the more formidable ones which have been used for neurophysiologic disturbances in man.

DR. MATTHEW T. MOORE: I want to ask Dr. Wycis whether the peculiar sucking and puckering movements the patient showed were present prior to the last operative procedure.

DR. FRANCIS C. GRANT: I should have been much more impressed with this particular procedure if Dr. Wycis had dug up almost any of my surgical ghosts but this one. I had operated on this woman in 1941, and she is one of those patients with whom one is very sorry to have had any dealings. I was unhappy about her case from the start. She had a bad family background; she is a pretty stubborn woman. She goaded me into operating on her. I was not particularly

enthusiastic about it. She then haunted my office for the next three years until I told my secretary that in no circumstances would she be allowed to come into the office.

I shall be much more interested in this case and the results—which are extraordinarily satisfactory so far—a year hence than I am now. If Dr. Wycis and Dr. Spiegel can make the cure stick in this particular case, I shall be very much interested and, I may add, mildly amazed, for I think there is a good deal of functional overlay in this case.

I agree entirely with Dr. Scott; this is an extraordinarily interesting procedure, and it has been worked out on the finest physiologic and anatomic lines.

DR. F. H. LEWEY: This situation is slightly complicated by the fact that two types of treatment have been used simultaneously, the severance of the central trigeminal tracts for pain sense and the destruction of the mediodorsal nucleus of the thalamus. I do not see how one could prove the interruption of the quinto-thalamic tracts in this case, but I should like to know what the patient's attitude toward her pains has become after electrocoagulation of the thalamic nucleus? Patients with frontal lobotomy do not mention their pains any more but complain bitterly when asked about them.

DR. GEORGE D. GAMMON: I should like to ask what bearing this operation has on the classic thalamic pain syndrome, and why they think this woman regained other cutaneous sensation but not pain?

DR. CHARLES G. RUPP: I was wondering how the authors would make the localizations in their experiment if they had a case in which the pineal gland was not visualized.

DR. A. M. ORNSTEEN: I believe this is the only patient on whom the operation has been performed; am I correct?

DR. HENRY T. WYCIS: This is the first patient, but the operation has since been performed on another.

DR. A. M. ORNSTEEN: If this case is the first, Oct. 30, 1947 should be a historical landmark, and this operation may take its place with the Frazier-Spiller operation of subtotal resection for trigeminal pain; it may be the Spiegel-Wycis era of mesencephalothalamotomy. I hope it is, and that we are writing the first page of the history of this era.

Dr. Grant's question about the psychogenic possibilities in this case reminds me of a woman who was a patient at the Temple University Hospital for many years with cephalalgia and who made four trips across the Atlantic to see Babinski. She was seen by many neurologists in Philadelphia over a period of thirteen or fifteen years; it was not until the vertex of her scalp was cut and she was shown, when she came out of the light anesthesia, a piece of wet catgut and was told that this was the nerve which had given her the pain that she was relieved.

A needle going through the vertex in this case may have the same suggestive value if Dr. Grant's idea holds in the follow-up of this patient. I say this facetiously. I am really more sincere about my first remark, that this may be a new era for the relief of pain. I hope that this is a prognostication.

DR. SHERMAN F. GILPIN JR.: Dr. Grant's questions intrigue me. I do not know whether this is the place to ask him, but I should be interested in knowing why he did not want to operate. I realize he had plenty of reason to want to avoid her afterward, but what was it that made him reluctant to do the operation?

I am not clear as to the type of pain which this woman had when she came to Temple University Hospital. Did it occur in short paroxysms, with periods of freedom between? Did she have a psychiatric survey before she was operated on? If so, what was the result?

DR. FRANCIS GRANT: May I answer your first question? When I saw this woman first, I thought she had trigeminal neuralgia. There was not much doubt about the diagnosis. As I recall, I blocked the second or the third division.

DR. HENRY T. WYCIS: I think you got all three divisions at first.

DR. FRANCIS GRANT: I do not think so. I blocked either the second or the third.

DR. HENRY T. WYCIS: She stated that the entire face became numb.

DR. FRANCIS GRANT: Sometimes I am better than I think. I don't often get complete block from an attempt at a single division. Anyway, we blocked either the second or the third division, and she had relief for a while. Then she came back with what I thought was trigeminal neuralgia. She had stabbing pains with a trigger zone, and so forth and so on. The pain was relieved after the injection of alcohol, and she was relieved for, as I recollect it, rather a shorter time than I had expected. Then she came back, and we operated on her, with the usual anesthesia of the face. Then she began to have pain in the anesthetic area. I have seen similar cases before. Every one who operates on the trigeminal nerves sees them. She kept on being such a continual nuisance, coming in with the complaint of pain and practically putting her head down on my desk and crying, with her husband fluttering in the background, trying to do something for her, that I became suspicious of the whole situation, got him off in a corner and had a bit of a chat with him. That threw such a different light on the picture that I refused to see her. He was quite certain that when she wanted to do anything she did not have any pain and that when she did not want to do something she had a great deal of pain.

I may not have been as serious as I might have been in speaking about the work of Dr. Spiegel and Dr. Wycis. If we have any solution to these paresthesias that follow section of the sensory root, we have made a tremendous step ahead. The difficulty with the operation for major trigeminal neuralgia is the fact that in about 5 per cent of cases it produces this permanent anesthesia; the patient cannot tolerate it, and the situation is worse than before. If Dr. Spiegel and Dr. Wycis have produced, and can show us, a method by which that paresthesia can be relieved, we have the problem of major trigeminal neuralgia under better control.

This is a fine piece of work; it has been worked out with meticulous and scrupulous accuracy. My only objection is that I wish the authors had not picked out this particular case to prove their point. Give them another year, and if this woman is still free from her pain, I shall make public apology to them. Until then, I shall be inclined to doubt the permanency of results in this case.

DR. N. W. WINKLEMAN: May I ask the authors what the initial result has been in the second case?

DR. ERNEST A. SPIEGEL: I am grateful to all discussants for their comments, and I am particularly grateful for the criticism, which was expected. Frankly, I looked forward to all that Dr. Grant has said about this case. Dr. Wycis and I have discussed frequently the question of a psychogenic component in this case. In my introductory remarks, I mentioned that in some cases of this type one deals with two problems. One is the interruption of the afferent pathways; the second is the treatment of the psychogenic component. In some cases there is primarily an organic disturbance on which a psychogenic component may be superimposed. I do not wish in the least to deny that in this patient a psychogenic component may be superimposed on a primary trigeminal neuralgia. That there was primarily a more or less typical trigeminal neuralgia I am convinced, for a man like Dr. Grant, who has seen over 1,000 cases of this disease, performed the typical Frazier-

Spiller operation. If he had not made this diagnosis, he would not have operated. This reasoning supported me when I advised Dr. Wycis to try our operation on this patient.

The idea in this operation is to deal not only with the interruption of the centripetal pathways, but also with the second difficulty, and to produce such a state of mind in the patient that the fixation of the attention on the pain mechanism is, to a certain degree, interfered with.

There is one point that I think Dr. Wycis did not mention. The patient still has a slight degree of paresthesia sometimes in the region of the upper lip and the maxilla. She never mentions that, and one has to ask her before she mentions it. This may be comparable to what Freeman and Watts have observed after prefrontal lobotomy. If one asks her about it, she says it is not really pain, and she describes it as a sensation of zigzag movement in the face; but one has to ask her about it before she mentions it.

We made a similar observation in the second case, and that brings us to Dr. Winkleman's question. In that case we made a much more extensive, bilateral thalamic lesion, but apparently only an incomplete lesion of the spinothalamic systems. After the operation, there was a period in which there were disturbances of orientation for time. At this stage, when asked about the pain, the patient said she still had the pain. When we asked her why she did not complain about it, she said, "I don't feel like complaining about the pain." That was, however, a transitory state. We are not able as yet to evaluate the operative result in the second case, since the interval since operation is too short. I think I have also answered Dr. Lewey's question.

With regard to the thalamic syndrome, which originates in the ventrolateral nuclei, I always try to avoid as much as possible ventrocaudal and lateral extension of the lesion in order not to have thalamic pain.

With regard to Dr. Gammon's question as to why the patient regained sensation, she had only a unilateral lesion; so the pathways on the opposite side are still functioning. Since there are homolateral, as well as crossed pathways, there is ample opportunity for compensatory mechanisms. Dr. Wycis will answer the inquiry with regard to the pineal gland.

DR. HENRY T. WYCIS: In answer to Dr. Grant's question, there is no doubt that this patient has a psychogenic component. When the patient was referred to me for relief of pain, it was exactly as Dr. Grant had stated; she insisted, "Please do something for me." This procedure was, therefore, carried out as a last resort.

In answer to Dr. Rupp's question: If the pineal gland is not visualized, one must resort to encephalography. In the group of cases which we intend to report later, practically half the patients had to be subjected to encephalography. Then the relation of the needle to the third ventricle and aqueduct of Sylvius, as outlined by the encephalogram, is established. Frequently, when we do not see the pineal gland on the routine roentgenogram of the skull, it may be visualized on the encephalogram.

I am grateful to Dr. Ornsteen and Dr. Michael Scott for their comments on the paper.

Peripheral Nerve and Root Disturbances Following Vaccination Against Smallpox. DR. N. W. WINKLEMAN (by invitation).

This paper was published in the October 1949 issue of the ARCHIVES, page 421.

DISCUSSION

DR. A. M. ORNSTEEN: This is really the début of a future member of the Philadelphia Neurological Society, and we should welcome him! I take the opportunity to do so.

When Dr. Winkleman was half through the paper, I wondered whether he was going to identify this condition as a specific smallpox neuritis, and I was relieved when he compared it with the serum reactions of various sorts. The reaction best known clinically is that to the immunizing dose of tetanus antitoxin. It is not common, but if one has seen half a dozen cases in a number of years one is impressed with its importance, even though it is rare.

The reaction to rabies during the course of immunization or of treatment after a dog bite is closer, I believe, to the smallpox type of neuropathy or radiculitis than is the serum reaction of tetanus, which is an allergic process, as Dr. Winkleman pointed out, with symptoms of serum reaction. The radiculitis and encephalomyelitis complicating rabies treatment are closer to the smallpox type that Dr. Winkleman described than is the reaction to tetanus antitoxin.

The incidence of 5 cases seen in the Neurological Institute at a time when there were 6,000,000 vaccinations shows how rare the condition is; it would be more impressive to say that the disturbance is due to a constitutional vulnerability than to anything pertaining to the vaccine itself or to the type of infection.

I wish to say that the presentation is deserving of commendation from the older members of the society.

DR. N. W. WINKLEMAN: I believe the neuropathy seen in association with rabies is related to this entity. As to its exact relation, I do not want to make any definite statement at this time.

Neural Toxicity from the Sulfonamides. DR. GEORGE D. GAMMON and DR. E. B. SCHOENBACH.

The sulfonamide compounds which produce neural signs most frequently are uliron® (4′-[dimethylsulfanyl]-sulfanilide), sulfanilylsulfonilamide and sulfamethylthiazole. Thirteen cases in which the last-named preparation was used are reported among German army personnel. The syndrome is a flaccid motor weakness below the knees, which develops rapidly. It reaches a peak within several hours to several days. Spontaneous sensory symptoms are thereafter absent, and objective tests show little loss. In about half the cases there is involvement of the hands, with characteristic wasting of the thenar muscles and the first, second and third interosseus muscles. Recovery is minimal, slow and incomplete. The spinal fluid is normal.

Periarteritis nodosa, as described by Arnold Rich, was observed in 2 American civilians. One had symmetric multiple neuritis, and the other asymmetric "multiple mononeuritis."

Cases of sulfamethylthiazole poisoning were clinically distinct from the more prevalent diphtheritic neuritis.

DISCUSSION

DR. A. M. ORNSTEEN: I am much interested in Dr. Gammon's hypothetic considerations of the cause and physiopathogenesis. The case I reported in 1938 with Molitch was one of neuritis due to sulfanilamide poisoning. I stressed then, and referred to cases previously reported, that the clinical feature of the neuropathy was a muscular dystrophy with involvement of the proximal portion of the limbs. Our patient "climbed up on himself" like a patient with dystrophy. He had difficulty in getting his arms over his head. There was no atrophy of the distal portions of the limbs. A decade ago I felt moved to say that the clinical picture

of sulfanilamide neuritis was similar to that of dystrophy. Now I hear they are all distal neuropathies. Is that to be explained by a difference in the drug or by a difference in reaction on the part of the patient? I have no idea. One must change one's original concept that the clinical picture of sulfanilamide neuritis is like that of dystrophy.

DR. GEORGE D. GAMMON: In the first case reported there were merely pains in the upper extremities; in the next optic neuritis resulted from sulfanilamide. In Dr. Ornsteen's case, and in another, there was bilateral axillary nerve paralysis. One of the earliest cases was reported by Janet, in Paris, in which there was paralysis of the muscles of the shoulder girdle and the pectoral muscles.

The earlier literature is to be found in the dermatologists' reports. They were treating gonorrhea with the sulfonamide compounds, which were toxic, and there is not much description of the patients. Dr. Ornsteen's case was unusual in several respects. The patient had gonorrhea, for which he received a long course of sulfanilamide therapy. Six weeks later he had onset of neuritis, with the weakness chiefly proximal; this advanced over a period of several weeks. It slowly progressed and then slowly regressed. There are few such cases in the literature, and in most of them the condition is the result of involvement of the spinal cord, rather than a typical peripheral neuritis. The other patients, who had neural complications from sulfanilamide and all the commonly used drugs, did not present the uniform picture that I described for sulfamethylthiazole. They had a more spotty reaction. Again, this might mean that they had a vascular involvement of the nerves.

DR. N. W. WINKLEMAN: Dr. Gammon, I have heard that of your 13 patients, 12 were treated for gonorrhea. Is that so?

DR. GEORGE D. GAMMON: Yes.

DR. N. W. WINKLEMAN: Dr. Ornsteen's patient also had gonorrhea. Are there many of the 179 cases recorded in the literature in which the neuritis resulted from therapy for other diseases? Sulfonamides are used for conditions aside from gonorrhea. They were originally used for pneumonia, for meningitis and for infections anywhere. I wonder whether there is a symbiosis, for this type of neuropathy does not seem to result from the use of sulfonamides for other diseases.

I was impressed by another point in your presentation, Dr. Gammon. You used the terms neuritis and myelitis, and then you showed us a cross section of a blood vessel with the appearance of an inflammatory condition. I wonder whether it was a true inflammatory process. In my experience, I have seen only 1 case of peripheral neuritis in which an inflammatory lesion appeared in the nerves themselves. For the most part, the condition would fall under the heading of neuropathy. I wonder whether your designation is correct. It might well be that the same type of reaction is present in the cord and in the roots and in the peripheral nerves. If so, it might or it might not come under the heading of allergy, although Dr. Ferraro only recently has included many of these processes with allergy.

DR. GEORGE D. GAMMON: The nomenclature is an "old-fashioned clinical" one. I had no intention of specifying an inflammatory reaction for this condition. From analogy with animal experimentation, it is a neuropathy rather than an inflammatory reaction, except in Rich's cases, in which there was a vascular syndrome.

The question concerning gonorrhea has been debated a great deal in the German and Scandinavian literature. The drugs sulfanilyl sulfanilamide and sulfamethyl-

thiazole were introduced into the treatment of gonorrhea. The first reports of neural toxicity began to appear within six months of their introduction. Therefore they were rarely used in treatment of other diseases.

In the few cases in which sulfamethylthiazole was used in the United States, for example at the Mayo Clinic, other conditions besides gonorrhea were treated, with toxic reactions, which were described as anterior horn cell disease. I think there were 3 cases of that sort. The toxicity does occur with conditions other than gonorrhea, although some of the German physicians I spoke to said that it never did.

I should have put it the other way around: Gonorrhea is singularly free from neural complications. The other diseases, such as lupus, may have many complications; so it is difficult to ascribe the result to the drug or to the disease or to an interaction of the two. However, a combination of factors is probably important in some cases.

DR. N. W. WINKLEMAN: There are three points that I should like to emphasize. First, a factor which has already been mentioned as contributory to the neuropathy following the sulfonamide therapy of gonorrhea is the gonorrheal infection. The etiologic and clinical similarities between the subject of my paper, the postvaccinal and postserum neuropathies, and the subject of Dr. Gammon's paper, the postsulfonamide neuropathies, have already been mentioned. Therefore, let us apply what is known about the relation of one of these entities to the other. Some authors have suggested that a certain lack of resistance, either generalized or organ specific, appears to be involved in the production of these entities. Cole and Hurst reported on 2 patients with postvaccinal complications involving the nervous system, one of whom had pneumonia and the other severe furunculosis. These authors stated that in their experience systemic infections were frequently present in persons who presented the neurologic complications of serum and vaccine therapy. Fyfe and Fleming said that most of the patients with postvaccinal encephalitis they had seen had infections of the upper respiratory tract or generalized infectious processes.

Second, Dr. Ornsteen mentioned the case of neuropathy following sulfonamide and fever therapy for gonorrhea which he had previously reported. There have been reports of neuropathies following fever therapy alone.

This brings me to the third factor, which I believe is the vital one. The neuropathies follow not only serum therapy, which, as I stressed in my paper, belongs to the serum neuritides, and use of the sulfonamides but also snake and insect bites, severe sunburn, severe infections, penicillin therapy and many debilitating diseases. The fundamental problem is to find the common denominator. From the pathogenic standpoint, these neurologic complications fall into two groups—extrinsic and intrinsic. The former involves the introduction of a foreign substance into the organism, which acts either as an antigen to produce antibodies or as a highly specific hapten, necessitating combination with a substance in the nervous system to render the hapten antigenic. The intrinsic type probably involves the alteration of a substance in the nervous system, rendering it antigenic. In both cases, when the antibody titer reaches a certain level, there occurs an antigen-antibody reaction. Many basic facts, however, are not known. What substance in the nervous system is involved in these reactions? Where is it located, and what are its chemical and immunochemical properties? Does the reaction involve the nerve tissue itself or its blood vessels? Finally, what can be done to reverse this reaction? There are many questions to be answered before the neurologic complications of serum and drug therapy will be understood.

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